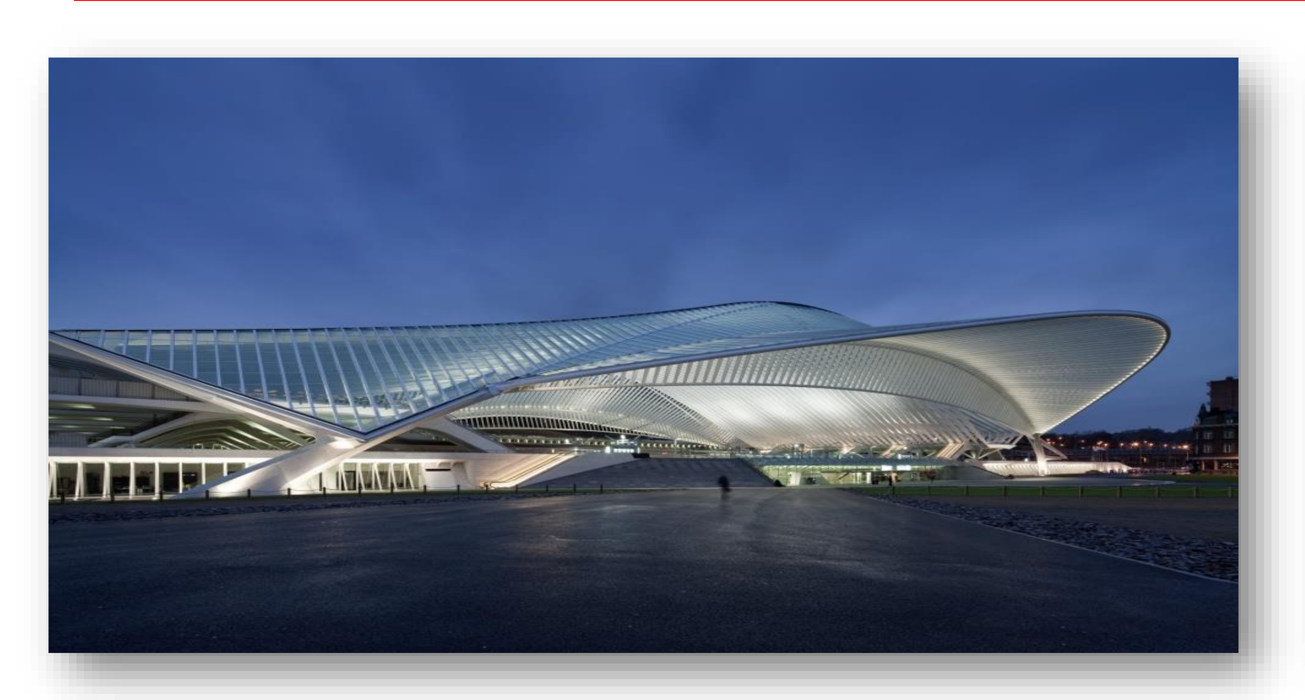
Master Class HF 2017
Le Traitement dans l'insuffisance cardiaque





Dr Pierre Troisfontaines
Centre de l'Insuffisance cardiaque
CHR de Liège





TRAITEMENT MEDICAMENTEUX



Buying cigarettes at the hospital bedside in the 1950s. @oldpicsarchive

Recommandations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 1.2 Level of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Prévenir ou retarder le développement d’une IC

Recommendations	Class[a]	Level[b]	Ref[c]
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A	126, 129, 150, 151
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A	137–140, 152
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C	131–134
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C	130, 141, 153–155
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B	130
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A	5, 144, 145
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.	I	B	5
ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.	IIa	A	142
Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.	I	B	146

Buts du traitement de l'IC

- ✓ **Améliorer la symptomatologie**

  Diurétiques, digitaliques, IEC / ARBs, vasodilatateurs…

- ✓ **Améliorer la survie, le pronostic**

  IEC / ARBs, bêtabloquants, spironolactone

- ✓ **Traitements étiologiques**

  Correction d'une valve, pontage,…

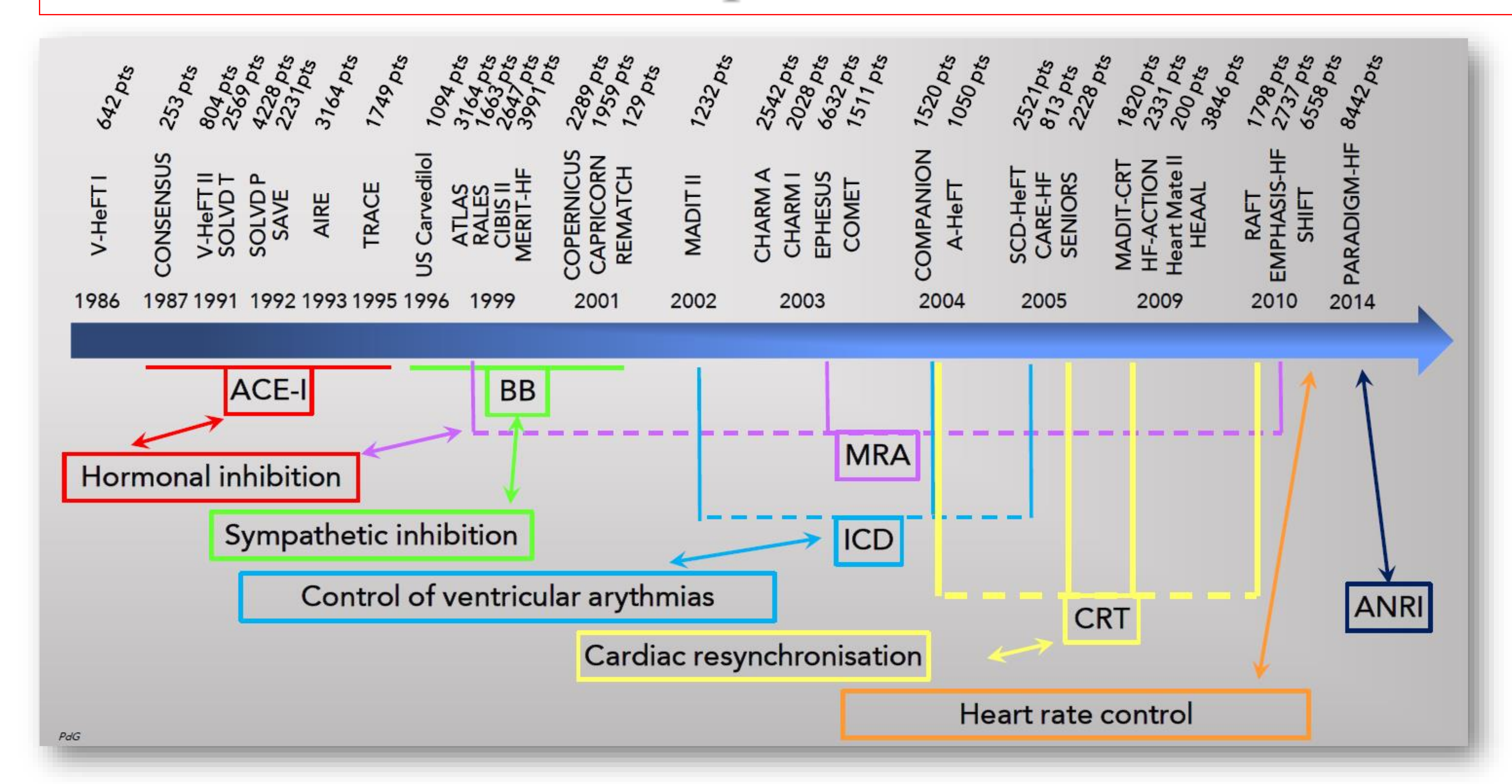
- ✓ **Traitements associés**

  Anticoagulants, anti-arythmiques, statines…



Prof. Gerasimos Filippatos: « *It's only in patients with* ***HFrEF that therapies have been shown to*** *reduce both morbidity and mortality."*

Etudes cliniques dans HFrEF



Traitement pharmacologique



2016 ESC Guidelines for heart failure;
European Heart Journal 20 May 2016,

! En Belgique, Ivabradine si Rythme sinusal > à 75 bpm (cf. INAMI)

FEVG≤ 40 %, NYHA-I à IV

IEC* + bêtabloquant

+ Diurétiques si congestion

(*ou ARA2 si intolérance)

FEVG ≤ 35 %

NYHA ≥ 2

Discuter DAI

+ ARM

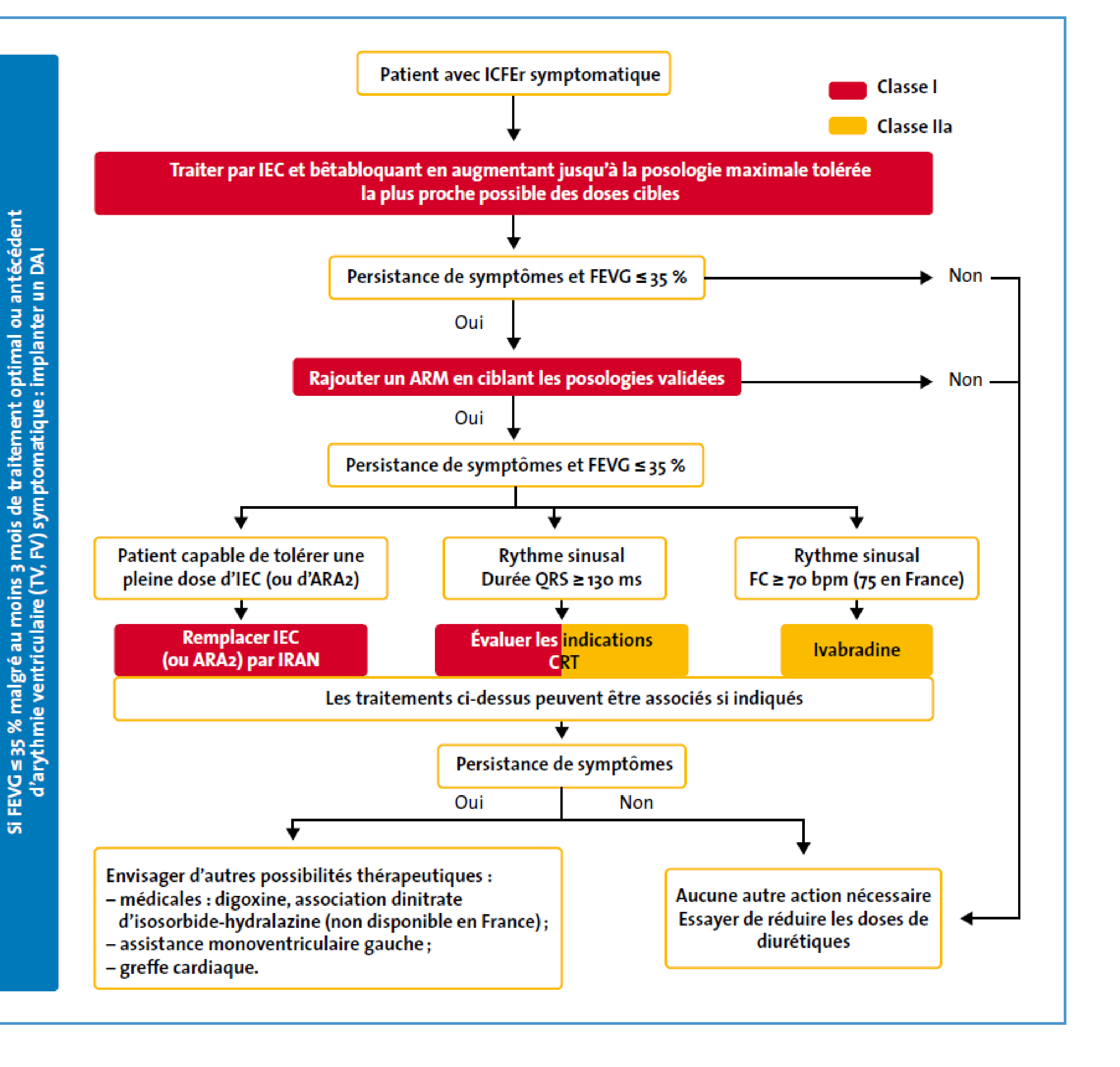
Réadaptation à l'effort

Persistance FEVG ≤ 35 % et NYHA ≥ II

- LCZ à place de l'IEC*
- Ivabradine si FC ≥ 70
- Pacemaker biV si QRS ≥ 130 ms
- Fer IV si ferritinémie basse

FEVG ≤ 30 %, NYHA ≥ IIIb

LVAD et/ou transplantation



Diurétiques pour traiter les symptômes et les signes congestifs
Si FEVG ≤ 35 % malgré au moins 3 mois de traitement optimal ou antécédent d'arythmie ventriculaire (TV, FV) symptomatique : implanter un DAI
Patient avec ICFEr symptomatique
Classe I
Classe IIa
Traiter par IEC et bêtabloquant en augmentant jusqu'à la posologie maximale tolérée la plus proche possible des doses cibles
Persistance de symptômes et FEVG ≤ 35 %
Non
Oui
Rajouter un ARM en ciblant les posologies validées
Non
Oui
Persistance de symptômes et FEVG ≤ 35 %
Patient capable de tolérer une pleine dose d'IEC (ou d'ARA2)
Rythme sinusal
Durée QRS ≥ 130 ms
Rythme sinusal
FC ≥ 70 bpm (75 en France)
Remplacer IEC (ou ARA2) par IRAN
Évaluer les indications CRT
Ivabradine
Les traitements ci-dessus peuvent être associés si indiqués
Persistance de symptômes
Oui
Non
Envisager d'autres possibilités thérapeutiques :
– médicales : digoxine, association dinitrate d'isosorbide-hydralazine (non disponible en France) ;
– assistance monoventriculaire gauche ;
– greffe cardiaque.
Aucune autre action nécessaire
Essayer de réduire les doses de diurétiques

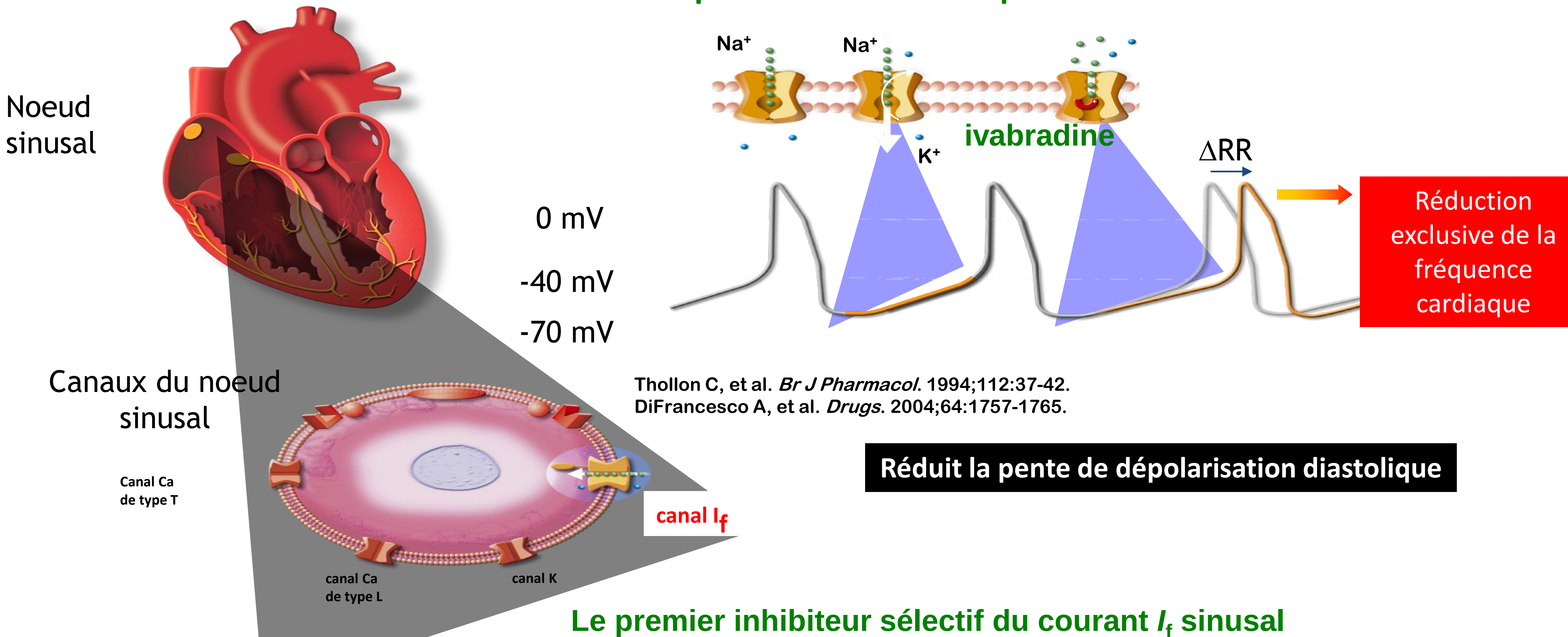
	Starting dose (mg)	Target dose (mg)
ACE-I		
Captopril[a]	6.25 t.i.d.	50 t.i.d.
Enalapril	2.5 b.i.d.	20 b.i.d.
Lisinopril[b]	2.5–5.0 o.d.	20–35 o.d.
Ramipril	2.5 o.d.	10 o.d.
Trandolapril[a]	0.5 o.d.	4 o.d.
Beta-blockers		
Bisoprolol	1.25 o.d.	10 o.d.
Carvedilol	3.125 b.i.d.	25 b.i.d.[d]
Metoprolol succinate (CR/XL)	12.5–25 o.d.	200 o.d.
Nebivolol[c]	1.25 o.d.	10 o.d.
ARBs		
Candesartan	4–8 o.d.	32 o.d.
Valsartan	40 b.i.d.	160 b.i.d.
Losartan[b,c]	50 o.d.	150 o.d.
MRAs		
Eplerenone	25 o.d.	50 o.d.
Spironolactone	25 o.d.	50 o.d.
ARNI		
Sacubitril/valsartan	49/51 b.i.d.	97/103 b.i.d.
If-channel blocker		
Ivabradine	5 b.i.d.	7.5 b.i.d.

Recommendations	Class[a]	Level[b]	Ref[c]
Diuretics			
Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.	I	B	178, 179
Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion.	IIa	B	178, 179
Angiotensin receptor neprilysin inhibitor			
Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA[d]	I	B	162
If-channel inhibitor			
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB).	IIa	B	180
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).	IIa	C	181
ARB			
An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE-I (patients should also receive a beta-blocker and an MRA).	I	B	182
An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate an MRA.	IIb	C	-
Hydralazine and isosorbide dinitrate			
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.	IIa	B	183
Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-I nor an ARB (or they are contra-indicated) to reduce the risk of death.	IIb	B	184
Other treatments with less-certain benefits			
Digoxin			
Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations).	IIb	B	185

« **En dessous de 0,5 ng/mL** de digoxine vous n'êtes pas efficace, **au-dessus d'1,2 ng/mL**, vous êtes dangereux », rappelait le **Pr Cohen-Solal**

Ivabradine: Inhibiteur sélectif des canaux If

Le courant I_f du noeud sinusal est le principal responsable de la fréquence cardiaque



Thollon C, et al. *Br J Pharmacol*. 1994;112:37-42.
DiFrancesco A, et al. *Drugs*. 2004;64:1757-1765.

Le premier inhibiteur sélectif du courant I_f sinusal

Robinson RB, DiFrancesco D. *Fundamental and Clinical Cardiology;* NY; Marcel Decker; 2001:151-170

Ivabradine en pratique

- Ivabradine :
  indiquée chez les patients insuffisants cardiaques :
  - Stade II à IV
  - FEVG ≤ 35%
  - Rythme sinusal > à 75 bpm (cf. INAMI)
  - **En supplément du traitement optimal: IEC, BB, MRA**

- Remboursement si prescrit par cardiologue ou interniste

SHIFT

(Systolic heart failure treatment with If inhibitor ivabradine trial)

- Étude randomisée, en double aveugle, évaluant l'effet ivabradine chez **6505** patients insuffisants cardiaque symptomatiques stade II à IV avec traitement jugé optimal, FEVG ≤ 35%, en rythme sinusal ≥ à 70/mn.
- **Critère primaire :**
  - Survenue d'un décès cardiovasculaire ou d'une hospitalisation pour aggravation de l'insuffisance cardiaque

Résultats : Diminution significative :

- ✓ 18% de la survenue d'un premier évéT n° crit. primaire
- ✓ 36% du risque de décès pour insuffisance cardiaque
- ✓ 11% du risque d'hospitalisation toute cause
- ✓ 26% du risque d'hospitalisation pour aggravation de l'IC
- ✓ 15% du risque d'hospitalisation de cause cardiovasculaire

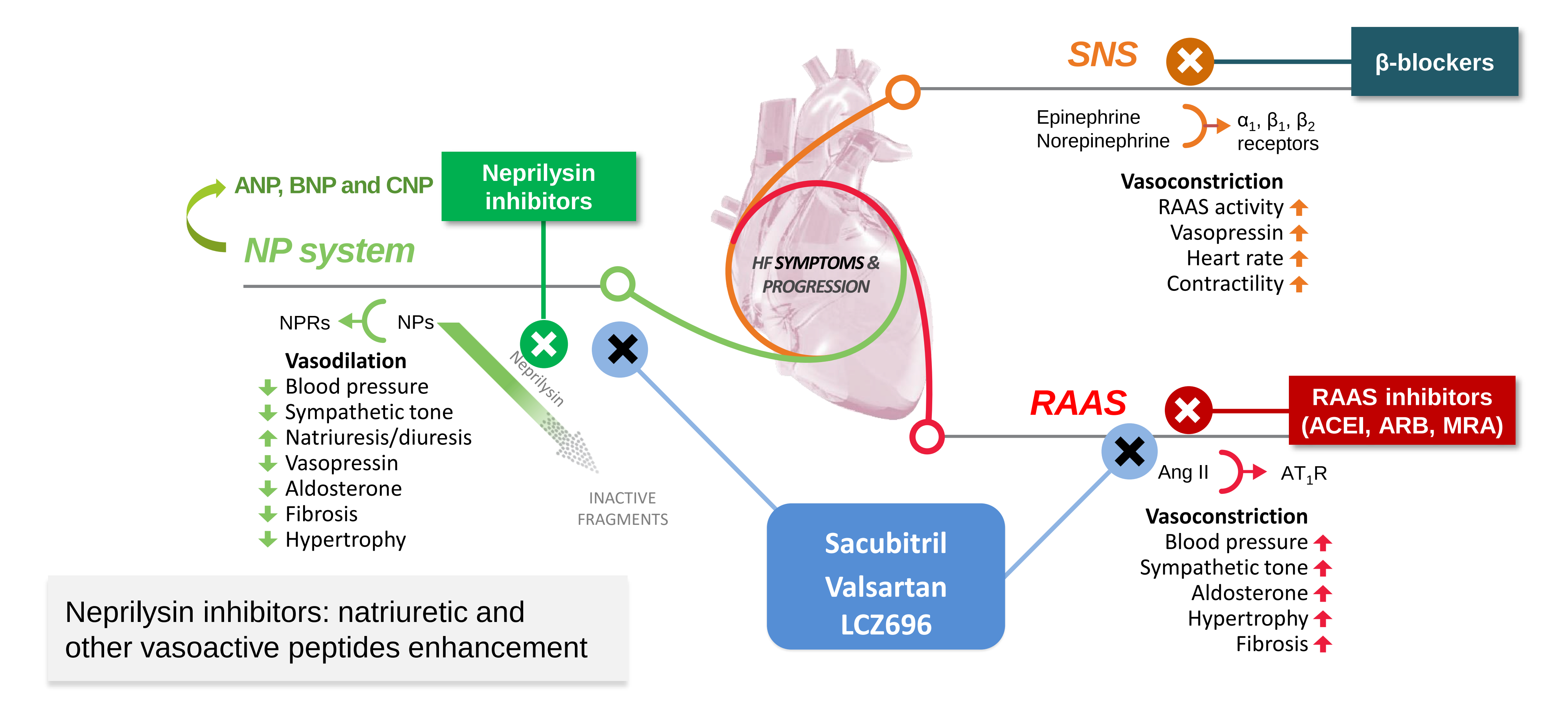
Swedberg K. Eur J Heart Fail. 2010;12:75-81
Swedberg K. Lancet. 2010 ;376:875-85 .

Optimalisation

Médicaments de première intention				
	Dose initiale mg/j	Dose cible mg/j	Dose max usuelle mg/j	Dose cible (nbre de prises)
IEC				
Captopril	6,25	50-100	150	2-3/jour
Cilazapril	0,5	1-2,5	5	1/jour
Enalapril	2,5	20	40	1-2/jour
Fosinopril	5	10-20	40	1/jour
Lisinopril	2,5	20-35	35	1/jour
Périndopril arginine/périndopril ter-butylamine	2,5/2	5/4	10/8	1/jour
Quinapril	5	40	40	2/jour
Ramipril	1,25	5-10	10	2/jour
Trandolapril post-IDM	0,5	4	4	1/jour
β-bloquants				
Bisoprolol	1,25	10	10	1/jour
Carvedilol	3,125	50 si poids < 85 kg 100 si poids > 85 kg	50 100	2/jour 2/jour
Metroprolol XR	12-23,75	190	190	1/jour
Nebivolol	1,25	10	10	1/jour
Médicaments de seconde intention				
	Dose initiale mg/j	Dose cible mg/j	Dose max usuelle mg/j	Dose cible (nbre de prises)
Antagonistes de l'aldostérone				
Spironaloctone	12,5	25-50		1/jour
Epléronone post-IDM récent	25	50		1/jour
ARA II				
Candesartan	4	32	32	1/jour
Losartan	12,5	50	150	1/jour
Valsartan	40	160	320	1/jour

H.A.S.
2015

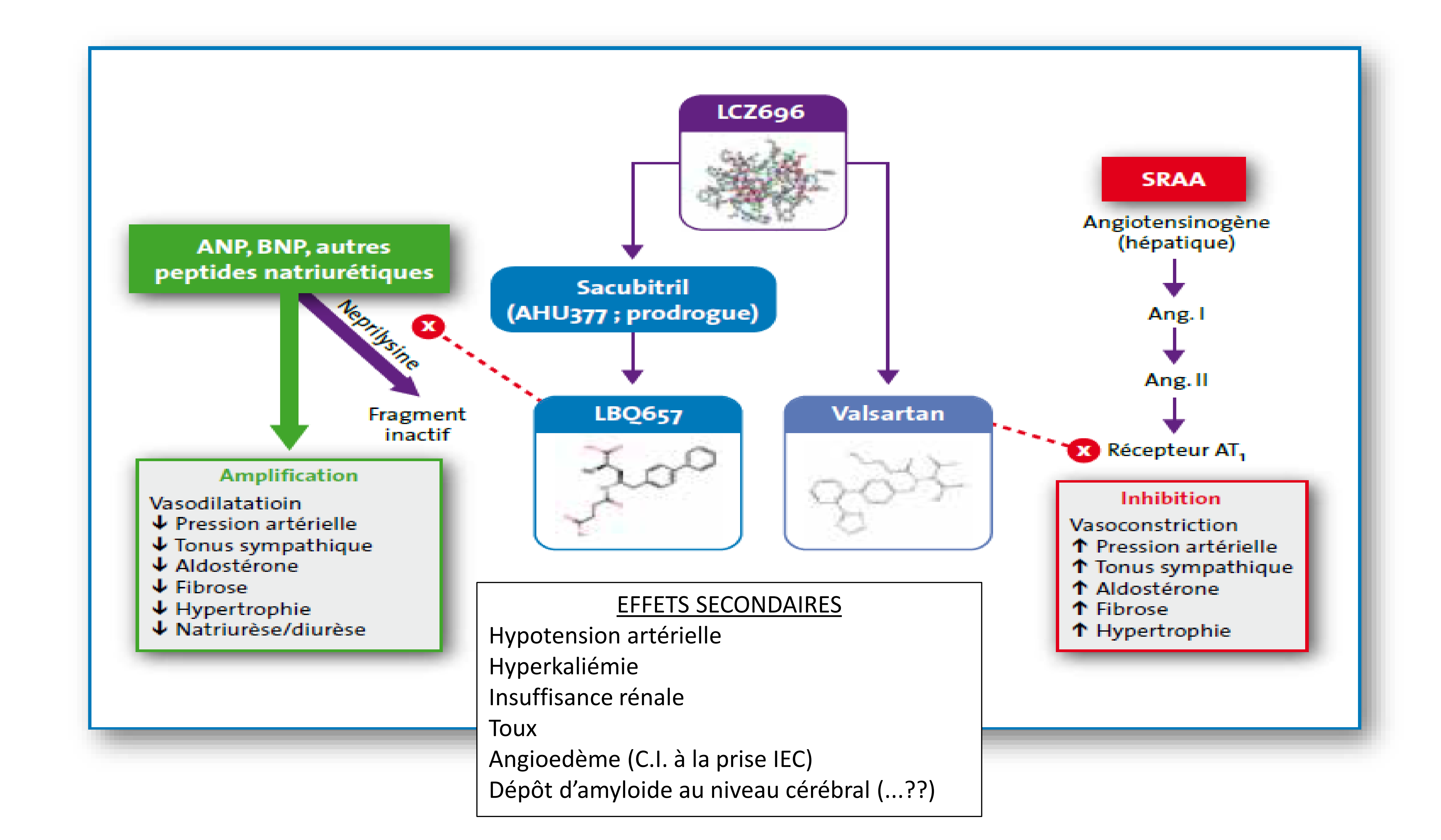
Evolution de l'approche pharmacologique :



Neprilysin inhibitors: natriuretic and other vasoactive peptides enhancement

Neprilysin inhibition combined with RAAS blockade

1. McMurray et al. Eur J Heart Fail. 2013;15:1062–73;
Figure references: Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan and Talbert. Pharmacotherapy 2002;22:27–42; Kemp and Conte. Cardiovascular Pathology 2012;365–71; Schrier and Abraham N Engl J Med 2009;341:577–85.


LCZ696
SRAA
Angiotensinogène (hépatique)
ANP, BNP, autres peptides natriurétiques
Néprilysine
Sacubitril (AHU377 ; prodrogue)
Ang. I
Ang. II
Fragment inactif
LBQ657
Valsartan
Récepteur AT1
Amplification
Vasodilatatioin
↓ Pression artérielle
↓ Tonus sympathique
↓ Aldostérone
↓ Fibrose
↓ Hypertrophie
↓ Natriurèse/diurèse
Inhibition
Vasoconstriction
↑ Pression artérielle
↑ Tonus sympathique
↑ Aldostérone
↑ Fibrose
↑ Hypertrophie
EFFETS SECONDAIRES
Hypotension artérielle
Hyperkaliémie
Insuffisance rénale
Toux
Angioedème (C.I. à la prise IEC)
Dépôt d'amyloide au niveau cérébral (...??)

PARADIGM-HF



Randomization
(N=8,442 patients with chronic HF [NYHA Class II–IV with LVEF **≤40%***]
and elevated NT-proBNP or BNP)

Double-blind randomized treatment period

Single-blind run-in period

Enalapril 10 mg BID**

LCZ696 100 mg BID†

LCZ696 200 mg BID‡

LCZ696 200 mg BID‡

Enalapril 10 mg BID§

Testing tolerability to target doses of enalapril and LCZ696

On top of standard HF therapy (excluding ACEIs and ARBs)

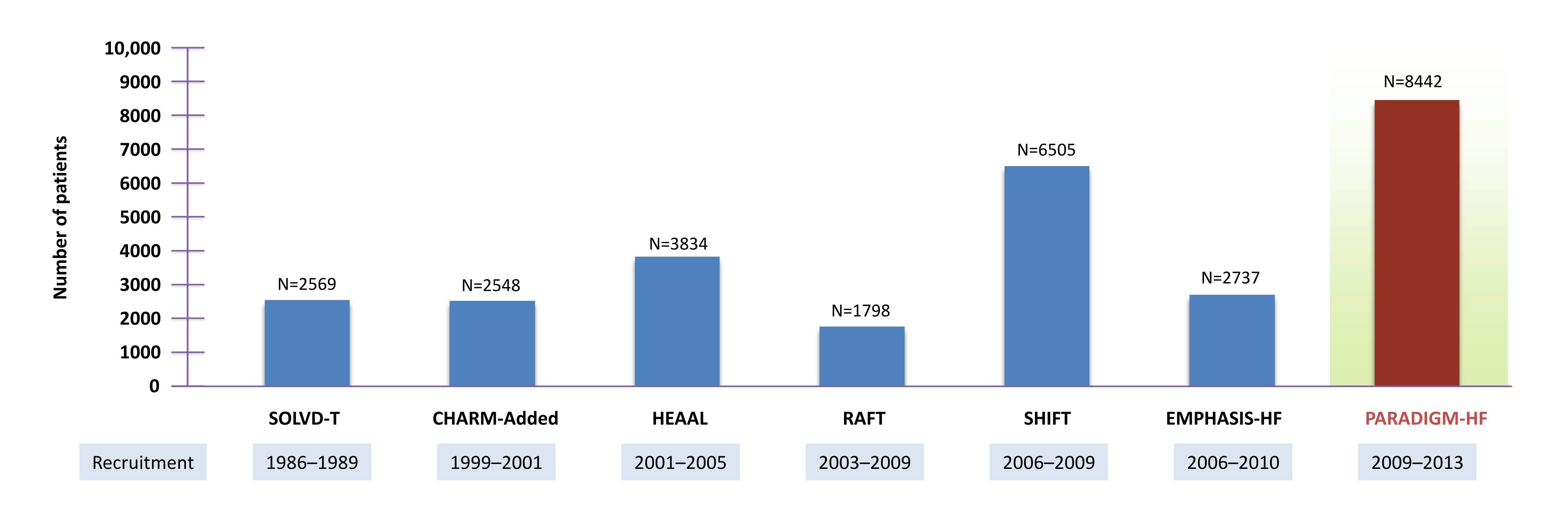
2 weeks | 1–2 weeks | 2–4 weeks | ~34 months (event-driven)

Primary outcome: CV death or HF hospitalization
(event driven: 2,410 patients with primary events)

*The ejection fraction entry criteria was lowered from ≤40% to **≤35%** in a protocol amendment on Dec 15,2010; **Enalapril 5 mg BID (10 mg TDD) for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI; †200 mg TDD; ‡400 mg TDD; §20 mg TDD. LVEF=left ventricular ejection fraction. There were 2 short washout periods during the run-in periods to minimize the potential risk of angioedema due to overlapping ACE inhibition and NEP inhibition at Visit 3 and Visit 5: (i) enalapril was stopped a day prior to starting LCZ696 at Visit 3 and (ii) LCZ696 was stopped a day prior to starting randomized study drug at Visit 5.

McMurray et al. Eur J Heart Fail 2013;15:1062–73

PARADIGM-HF: The largest mortality-morbidity trial in patients with HFrEF



McMurray et al. Eur J Heart Fail. 2014;16:817–25

PARADIGM-HF:

Characteristic*	LCZ696 (n=4187)	Enalapril (n=4212)
Age, years	63.8 ± 11.5	63.8 ± 11.3
Women, n (%)	879 (21.0)	953 (22.6)
Ischemic cardiomyopathy, n (%)	2506 (59.9)	2530 (60.1)
LV ejection fraction, %	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class, n (%)		
II	2998 (71.6)	2921 (69.3)
III	969 (23.1)	1049 (24.9)
SBP, mmHg	122 ± 15	121 ± 15
Heart rate, beats/min	72 ± 12	73 ± 12
NT pro-BNP, pg/mL (IQR)	1631 (885–3154)	1594 (886–3305)
BNP, pg/mL (IQR)	255 (155–474)	251 (153–465)
History of diabetes, n (%)	1451 (34.7)	1456 (34.6)
Treatments at randomization, n (%)		
Diuretics	3363 (80.3)	3375 (80.1)
Digitalis	1223 (29.2)	1316 (31.2)
β-blockers	3899 (93.1)	3912 (92.9
Mineralocorticoid antagonists	2271 (54.2)	2400 (57.0)
ICD	623 (14.9)	620 (14.7)
CRT	292 (7.0)	282 (6.7)

*mean ± standard deviation, unless stated

McMurray, et al. N Engl J Med 2014; ePub ahead of print: DOI: 10.1056/NEJMoa1409077.

Kaplan-Meier Estimate of Cumulative Rates (%)

40
32
24
16
8
0

Enalapril (n=4212) 1117

LCZ696 (n=4187) 914

HR = 0.80 (0.73-0.87)
P = 0.0000002
Number needed to treat = 21

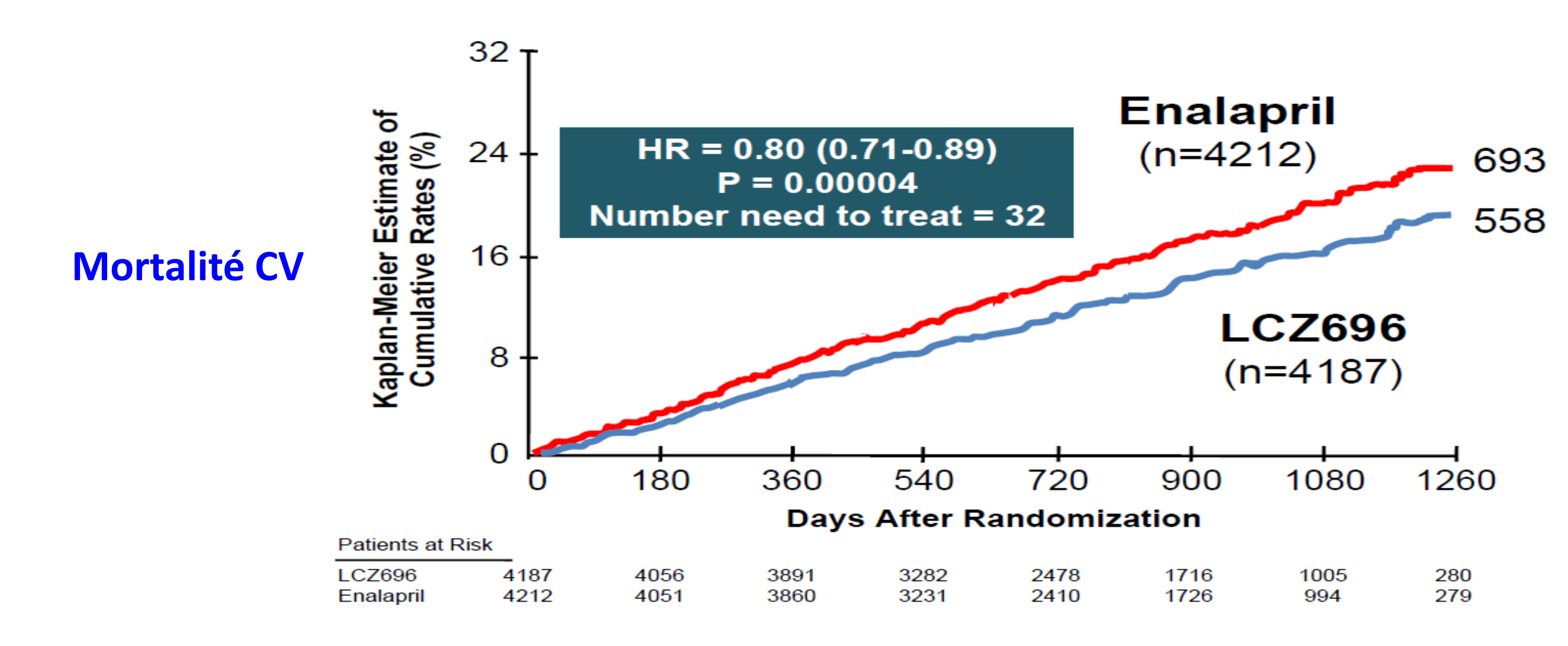
0 180 360 540 720 900 1080 1260

Days After Randomization

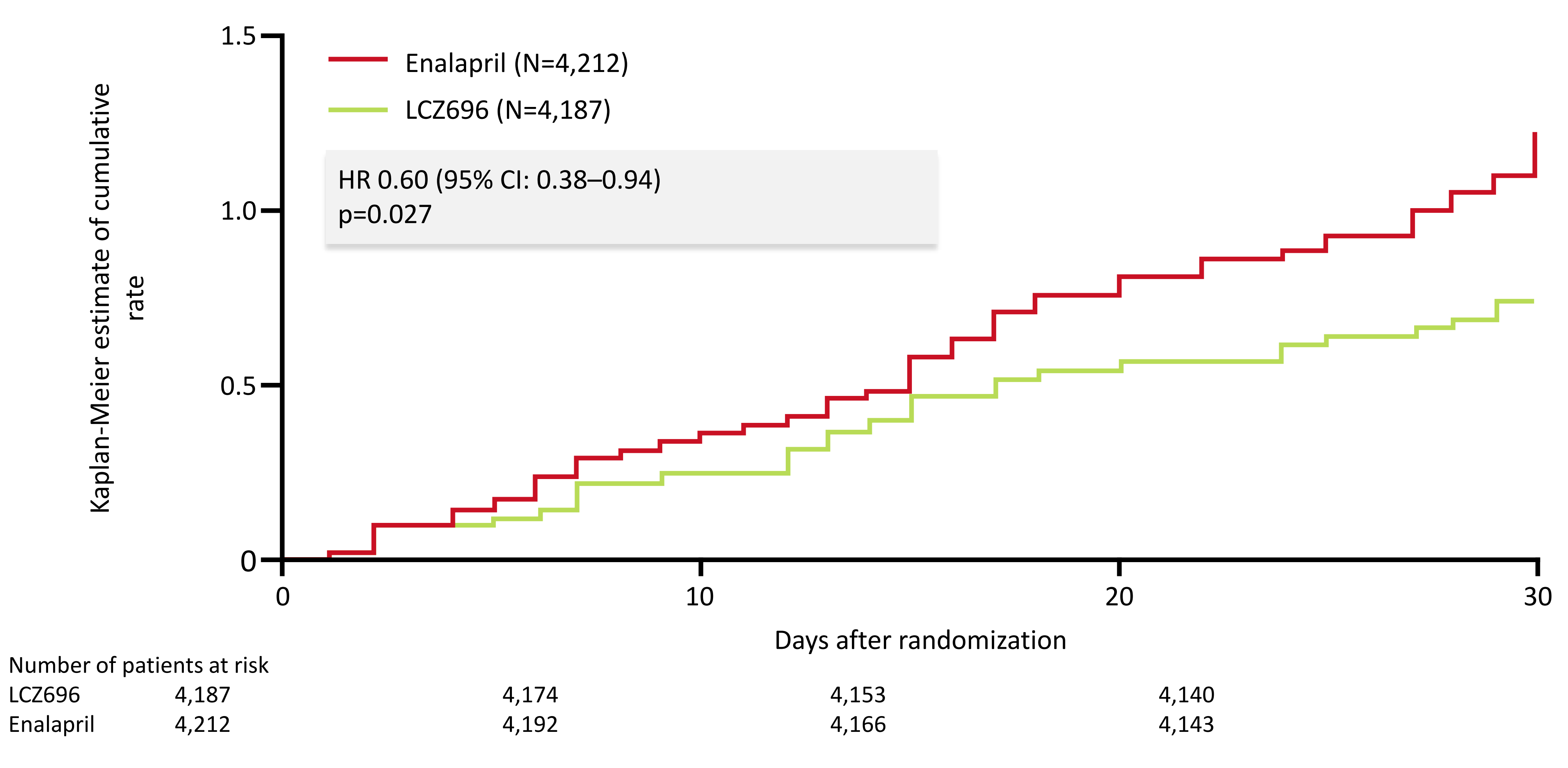
Patients at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

Critère combiné
Mortalité CV & HF hospitalisation

Mortalité CV



The reduction in heart failure hospitalization with LCZ696 was evident within the first 30 days after randomization



Shown is the Kaplan-Meier estimate of the cumulative probability of a first hospitalization for heart failure during the first 30 days after randomization. The analysis at 30 days was prespecified and also represented the earliest time point at which the difference between the LCZ696 and enalapril groups was statistically significant.

Packer et al. Circulation 2014; epub ahead of print: DOI: 10.1161/CIRCULATIONAHA.114.013748

Entresto: Indication, dosages et remboursement

Angiotensin receptor neprilysin inhibitor			
Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA[d]	I	B	162

- **Indication:**
  – Treatment of symptomatic chronic heart failure with reduced ejection fraction in adult patients
- **Dosages:**
  – Entresto ® 24 mg sacubitril/ 26 mg valsartan
  – Entresto ® 49 mg sacubitril/ 51 mg valsartan
  – Entresto ® 97 mg sacubitril/103 mg valsartan

24/26 mg
(sacubitril 24 mg and valsartan 26 mg)

49/51 mg
(sacubitril 49 mg and valsartan 51 mg)

97/103 mg
(sacubitril 97 mg and valsartan 103 mg)

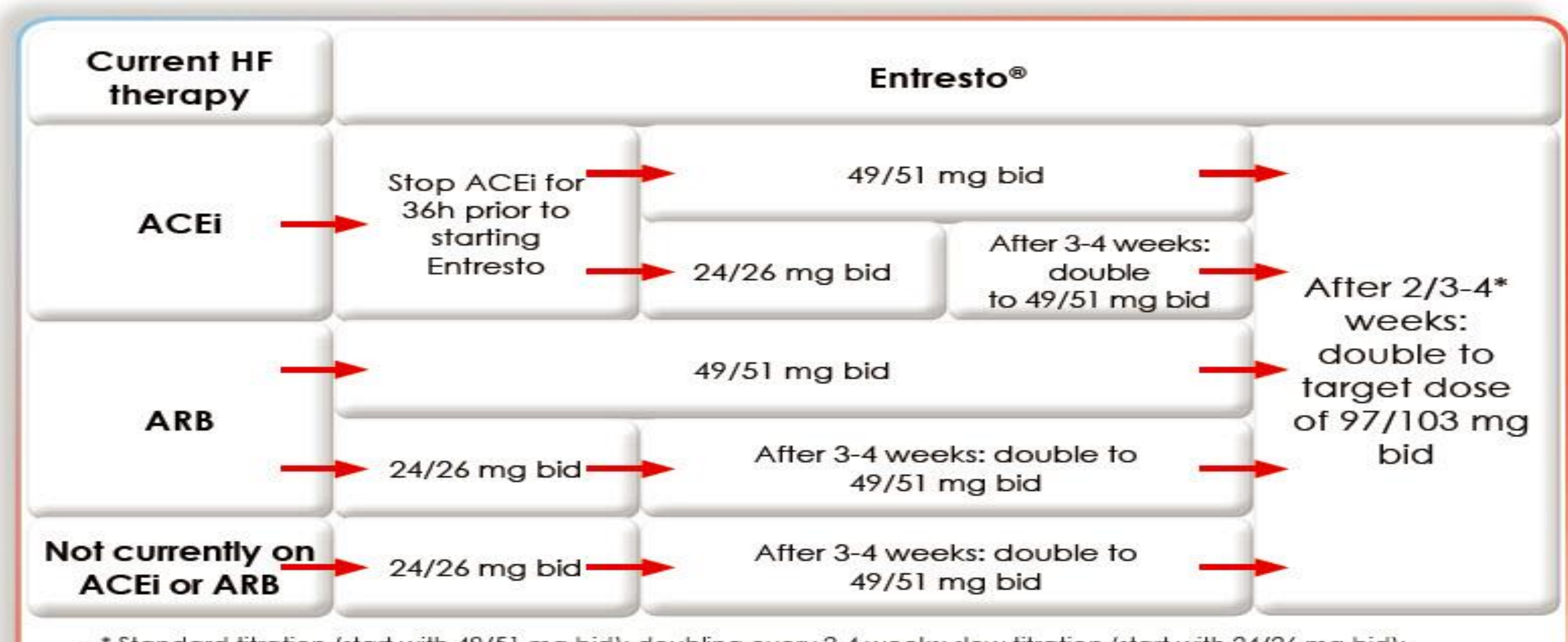
- **Critères de Remboursement au 1er Novembre 2016:**
  – NYHA II - IV
  – LVEF ≤ 35%
  – Optimal pre-treatment with ACEi/ARB
  – Initiation par un Cardiologue ou un interniste.

Sélection de la dose de départ:

Population	24/26 mg bid	49/51 mg bid	Should not be initiated
Currently on ACEi/ARB*			
≥ Threshold dose		X	
< Threshold dose	X		
Not currently on ACEi/ARB	X		
Renal function/ renal impairment (RI)			
Normal or mild RI: eGFR >60 ml/min/1.73m²		X	
Moderate RI: eGFR 30-60 ml/min/1.73m²	X		
Severe RI: eGFR <30 ml/min/1.73m²	X		
end stage renal disease			X
Kalaemia			
≤5.4 mmol/L		X	
>5.4 mmol/L			X
Systolic Blood Pressure			
<100 mmHg			X
≥100 - <110 mmHg	X		
>110 mmHg		X	
Hepatic impairment			
Mild		X	
Moderate (or AST/ALT >2x ULN)	X		
Severe			X
Biliary cirrhosis or choleostasis			X

* Entresto® is for oral use, must be swallowed with a glass of water, and may be administered with/without food.
For a complete list of contraindications, see section 2 below or section 4.3 of the SmPC.
table with thresholds below

Algorithme pour la Titration



Dosing and time



ACEi

STOP
ACEi
WAIT
36 h
GO
Start Entresto

Day 1 — Washout — Day 2/3

Moderate dose → 49/51 mg (2-4 weeks) → 97/103 mg

Low dose * → 24/26 mg (2-4 weeks) → 49/51 mg (2-4 weeks) → 97/103 mg

or

ARB

STOP
ARB
GO
Start Entresto

Day 1 — Day 1

Moderate dose → 49/51 mg (2-4 weeks) → 97/103 mg

Low dose * → 24/26 mg (2-4 weeks) → 49/51 mg (2-4 weeks) → 97/103 mg

* Renal or hepatic impairment, hypotension (SBP < 100-110 mmHg)

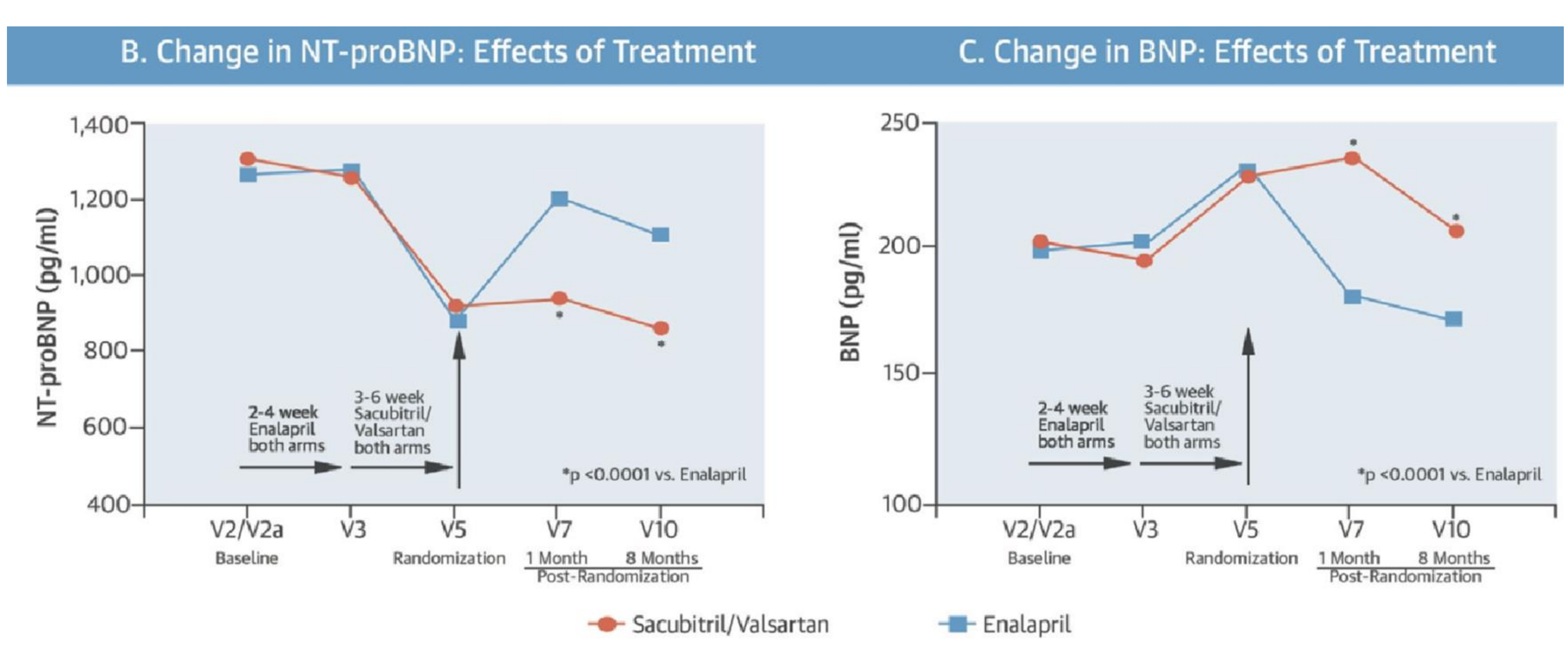
Twice daily intake

SmPC, Entresto, 16/06/2016

Interactions connues avec ENTRESTO

Interactions requiring precautions	
Medication	**Potential risk**
OATP1B1 and OATP1B3 substrates (Statins)	Increase of Statin concentration (AUC)
PDE5 inhibitor (e.g. Sildenafil)	Increase in lowering of the blood pressure
Potassium saving diuretics, supplements	Increase in serum potassium and creatinine
NSAIDs (+ COX-2 inhibitors)	Increase risk of worsening renal function
Lithium	Increase in serum lithium concentration and toxicity
Furosemide, Nitrates (Nitroglycerine), Metformin	Clinical relevance of those interactions are unknown but the clinical status of the patient should be evaluated
OATP and MRP2 transporters (Ciclosporin, Tenofovir, Ritonavir)	May increase the systemic exposure of Entresto®

Effect of LCZ696 (Sacubitril/Valsartan) on BNP and NT-proBNP



NT-proBNP remains an accurate measure of severity of HF in the setting of treatment with LCZ696 but BNP will not be reliable!

Zile et al. JACC 2016



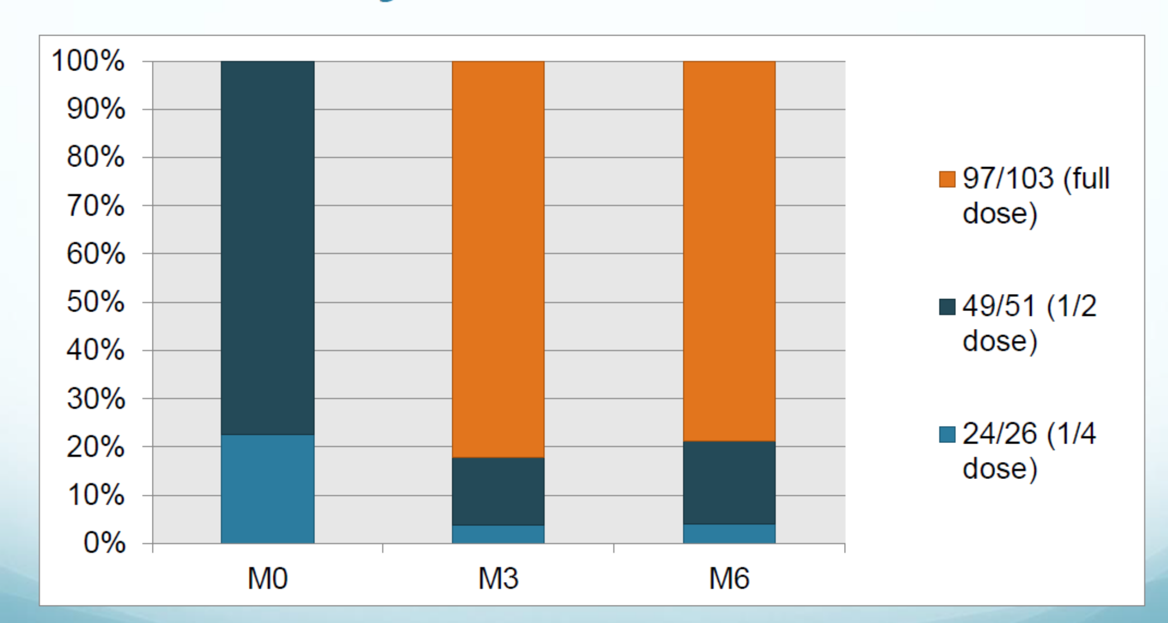
Expérience de Bordeaux

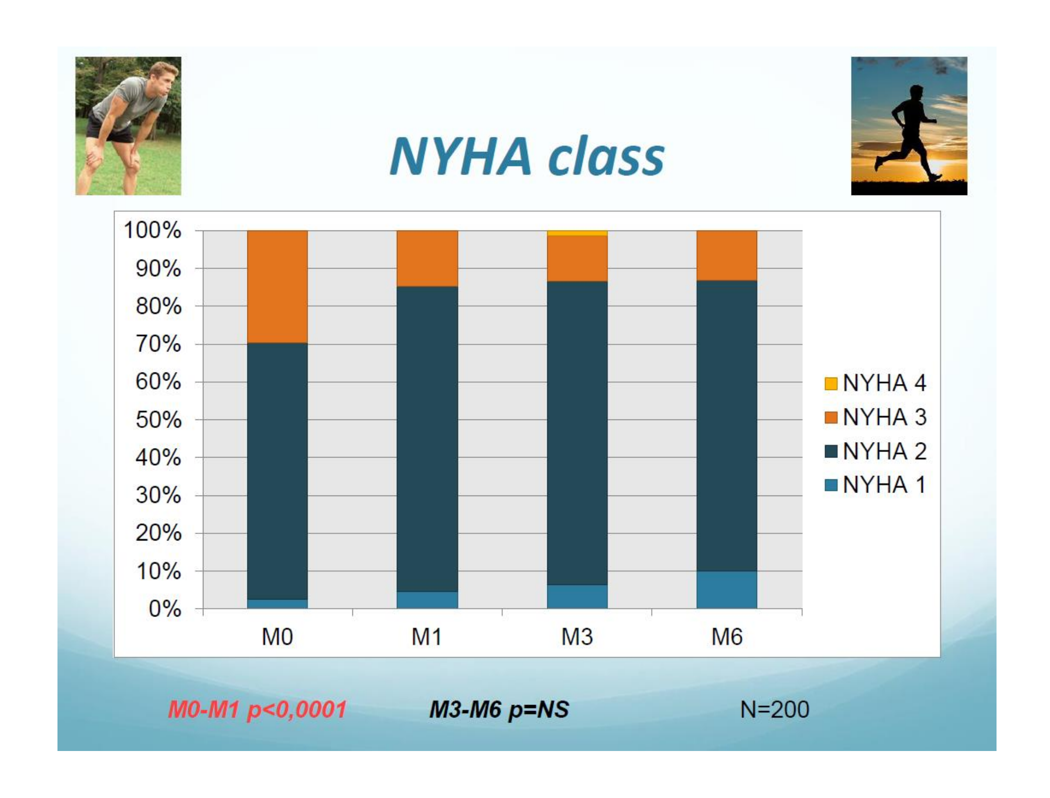
Dr Vincent MAURIN (Bordeaux)
JESFC - 12 Janvier 2017

DEMOGRAPHY	200	
Male	163	81%
Age (years)	**59**	
<60	85	42%
60-69	81	40%
70-79	33	17%
>80	1	1%
CLINICAL FEATURES OF HEART FAILURE		
Ischaemic	103	**51,5%**
Non-ischaemic	97	**48,5%**
MEDICAL HISTORY		
Hypertension	58	29%
Atrial fibrillation	59	29,5%
Diabetes	35	17,5%
Stroke	14	7%
Duration of heart failure > 1 year	167	**83,5%**
Diagnosis of heart failure < 3 months	19	**9,5%**
Hospitalization for HF in previous year	56	**28%**

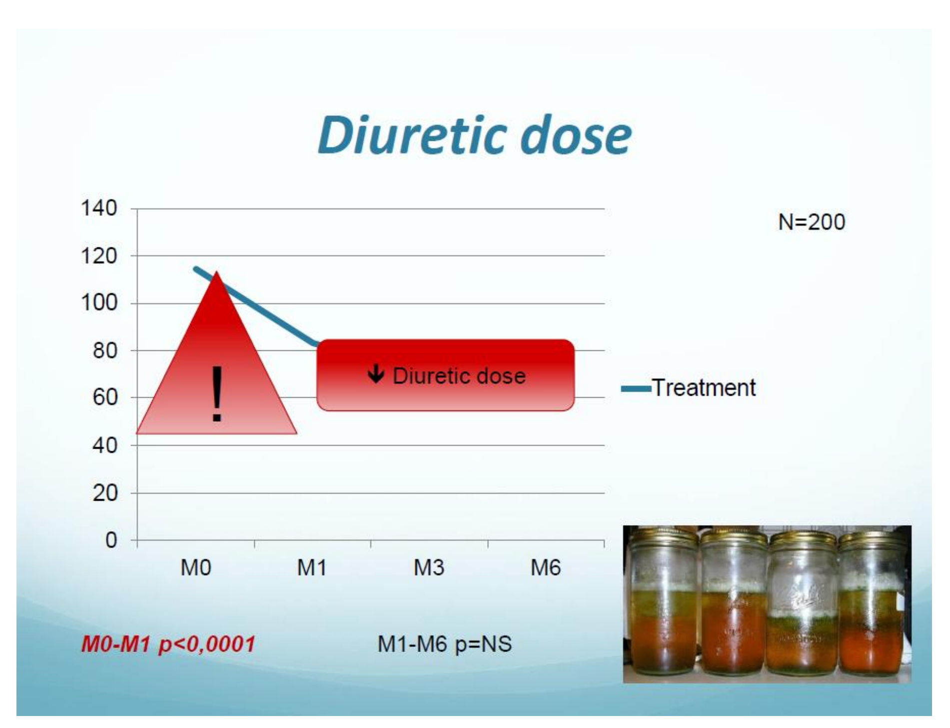
DRUG THERAPY	200		≥ 50% of target dose
ACEI/ARB	191	**96%**	**92%**
Beta-blocker	187	**93%**	**81%**
Mineralocorticoid antagonist	160	**80%**	**80%**
Implantable cardioverter–defibrillator (ICD)	75	37,5%	
Cardiac resynchronization therapy + ICD	56	28%	
Furosemide dosage (mg)	**114 mg**		
CLINICAL			
NYHA functional class			
I	5	**2,5%**	
II	136	**68%**	
III	59	29,5%	
IV	0	0%	
Six minute walking test (m)	461		
Systolic blood pressure (mmHg)	109		
Diastolic blood pressure (mmHg)	64		
BIOLOGY			
B-type natriuretic peptide (pg/mL)	**586**		
Serum creatinine (µmol/L)	108		
Hemoglobin (g/dL)	13.8		

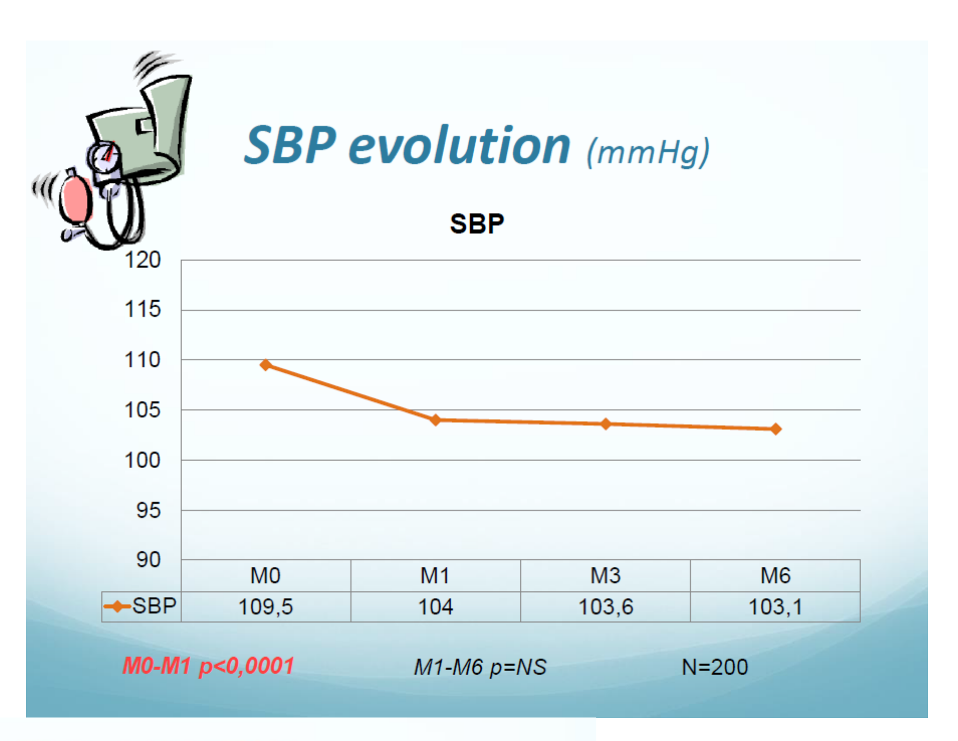
- **Well tolerated**
- **Functionnal benefit occurs in the first month**
- **Often with half dose**
- **Left heart remodeling**
- **Take care about diuretic dose**

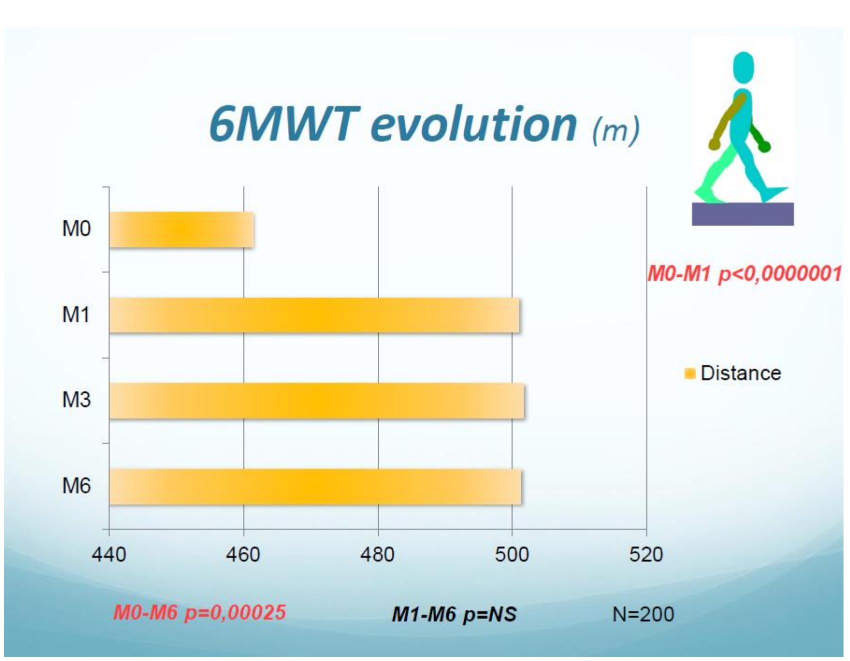




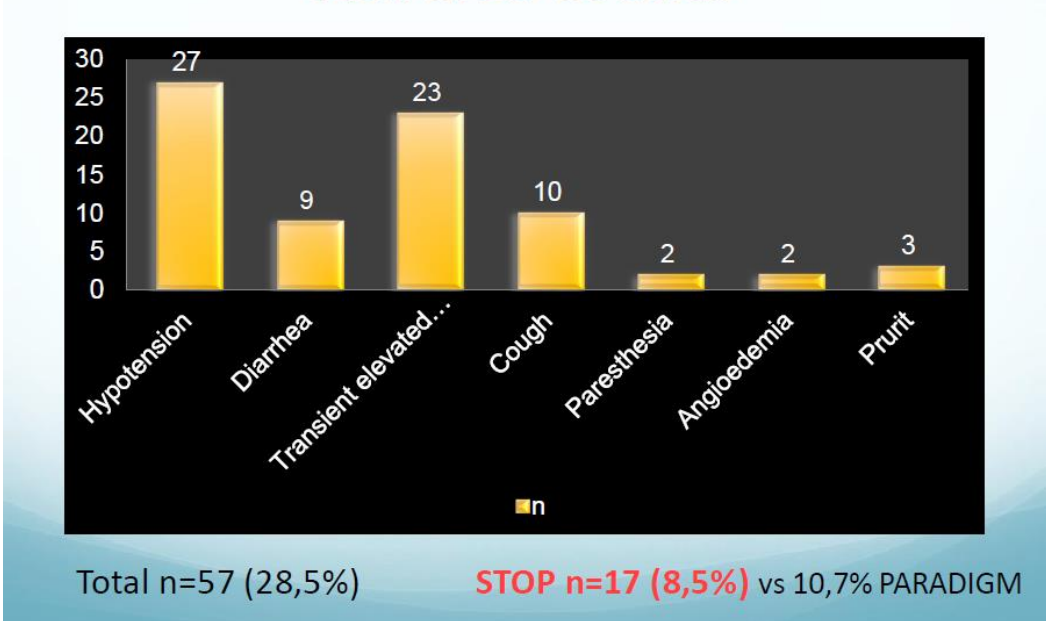
Dr Vincent MAURIN (Bordeaux)
JESFC 12 Janvier 2017


Diuretic dose
140
120
100
80
60
40
20
0
M0
M1
M3
M6
N=200
!
Diuretic dose
Treatment
M0-M1 p<0,0001
M1-M6 p=NS


SBP evolution (mmHg)
SBP
120
115
110
105
100
95
90
M0 M1 M3 M6
SBP 109,5 104 103,6 103,1
M0-M1 p<0,0001
M1-M6 p=NS
N=200


6MWT evolution (m)
M0
M1
M3
M6
440 460 480 500 520
M0-M1 p<0,0000001
Distance
M0-M6 p=0,00025
M1-M6 p=NS
N=200




Adverse events
30
25
20
15
10
5
0
27 9 23 10 2 2 3
Hypotension
Diarrhea
Transient elevated...
Cough
Paresthesia
Angioedemia
Prurit
n
Total n=57 (28,5%)
STOP n=17 (8,5%) vs 10,7% PARADIGM

Entresto: le bon profil

Recommended patient

- IC (HFrEF) Symptomatique chronique (LVEF ≤ 35%)
- NYHA Class II/III/IV
- SBP ≥ 100 mmHg
- GFR ≥ 30 ml/min/1.73m^2
- K < 5 mmol/L
- Pas de co-administration ACEi/ARB

Reimbursement **(1 Nov 2016)**

- Symptomatic chronic HFrEF **(LVEF ≤ 35%)**
- NYHA Class II/III/IV
- **Optimal pretreatment with ACEI/ARB**
- Initiation by cardiologist or internist

TITRATION BY GP AND CARDIOLOGIST

Entresto en pratique clinique

- Commencer au dosage 24/26 mg 2x/j **si** patient «naïf d'IEC/sartans» ou si sous des faibles doses d'IEC, équivalentes à 10 mg/j d'énalapril
- **«Wash-out»** de 36 heures après l'arrêt des IEC (risque d'angioedème)
- Titrer à la hausse (doubler) toutes les **2-4 semaines**
- Contrôler créatinine et ionos **1-2 semaines après début** traitement et changement de doses.
- **Adapter la dose de diurétique**

Traitement pharmacologique

! En Belgique, Ivabradine si Rythme sinusal > à 75 bpm (cf. INAMI)



2016 ESC Guidelines for heart failure; European Heart Journal 20 May 2016,

FEVG≤ 40 %, NYHA-I à IV

↓

IEC* + bêtabloquant — + Diurétiques si congestion

(*ou ARA2 si intolérance)

↓

FEVG ≤ 35 % → Discuter DAI ; → Réadaptation à l'effort

↓

NYHA ≥ 2

↓

+ ARM

↓

Persistance FEVG ≤ 35 % et NYHA ≥ II

↓

- LCZ à place de l'IEC*
- Ivabradine si FC ≥ 70
- Pacemaker biV si QRS ≥ 130 ms
- Fer IV si ferritinémie basse

↓ FEVG ≤ 30 %, NYHA ≥ IIIb

LVAD et/ou transplantation

Béta-bloquants en pratique

- Initié à très faible dose, avec surveillance de la PA et de la FC.
- Augmenté par paliers successifs, à intervalle d'1 à 2 semaines.
- **Hypotension asymptomatique : ne rien faire.**

Mais Vérifier l'absence de vasodilatateurs (antag.Ca++, nitrés,…) ou la posologie des diurétiques.

- **Bénéfice après 3 à 6 mois.**

ß-bloquants et …	Bloc A-V	Bradycardie	Hypotension/ Fatigue
Prudence si	I-II	< 60 bpm	< 90 mmHg
X ½ si	-	< 50 bpm sympto	Sympto
Stop si	II-III	< 50 bpm sympto	Sympto

IEC ou Sartans en pratique…

- Initié à faible dose, avec surveillance de la PA ;
- Augmenté par paliers successifs, à intervalle d'1 à 2 semaines minimum, sous contrôle de la PA
- **Biologies** 1 à 2 semaines après introduction
  et 1 à 2 semaines après dose maximale
- Suivre créatinine et potassium jusqu' à un **plateau**

Tolérer une ↑ créatinine jusqu'à 20-30 %

Ne sont pas des contre-indications:

- Insuffisance rénale modérée
  (Créatinine ≤ 25mg/l)
- **Tolérer** HypoTA (≤ 90 mmHg) asymptomatique

mais essayer de diminuer les diurétiques ou autres hypotenseurs
(antag.Ca++, nitrés,…)

Attention aux AINS

IEC ou Sartans en pratique…

Sartans et …	K+	Créatinine	PA
Prudence si	> 5 meq/l	> 25 mg/l	< 90 mmHg ou sympto
x ½ si	> 5,5 meq/l	> 30 mg/l ou > 50 %	Sympto
Stop si	> 6 meq/l	> 35 mg/l ou > 100 %	Sympto

- Prudence avec diurétiques d' épargne K+, Suppl. K+…
- Hypotension asymptomatique : ne rien faire
- Biologies 1 à 2 semaines après introduction
  et 1 à 2 semaines après dose maximale
- Suivre créatinine et potassium jusqu'à un plateau

Administration initiale et surveillance des anti-aldostérones

Chez les patients dès le stade II, malgré traitement optimal (diurétiques, IEC, BB)
si K+ < 5mMo/l, Créat < 25mg/l.

débuter avec 12.5- 25 mg Aldactone,

❖ **Contrôle créat. et K+ après 4 à 6 jours, puis 4 semaines**

- **si 5 < K+ < 5.5 => réduire de moitié,**
- **si K+> 5.5mMol/l ou Créat > 35mg/l => arrêt**

❖ **Contôle ionogramme et créatinine:**

- Tous les mois pendant 3 mois puis tous les 3 mois pendant 1 an puis au moins tous les 6 mois
- Lors d ’un événement pouvant modifier la kaliémie (fièvre, diarrhée, canicules, AEG)

Résistances aux diurétiques

- Augmenter les doses de diurétiques de l'anse (Furosémide ou Bumétamide)
- Fractionner les prises de diurétiques 2 à 4 prises/j
- Passer par voie intra-veineuse
- Assurer un régime hyposodé
- Association d'un thiazidique
  si GFR >30 ml/min
- Association de spironolactone/éplérénone

Suivi biologique en pratique…

- Biologie complète au minimum 2 fois/an
- Surveillance adaptée (sévérité, comorbidités,..)

- Selon évolution clinique et en fonction des modifications de traitement, de fièvre, de GE, de déshydratation,…

- Lors de toute modification de traitement :

(natrémie, kaliémie, créatinémie, urée)
  - 1 à 2 semaines après introduction IEC ou Sartans ou LCZ696
  - 1 à 2 semaines après dose maximale
  - Suivre créatinine et potassium jusqu'à un plateau

Si AVK : INR au moins une fois par mois

MÉDICAMENTS À ÉVITER DANS I.C.



Médicaments

- Anti-arythmiques (classe Ic)
- Certains inhibiteurs calciques (vérapamil, diltiazem)
- Corticostéroïdes (Rétention hydrique et sodée)
- AINS et coxibs (Rétention hydrique et sodée)
- Metformine (Risque d'acidose lactique)
- Lithium et antidépresseurs tricycliques
- Glitazones
- Macrolides et certains antimycotiques (allongement de QT)
- Antihistaminiques (allongement de l'espace QT)
- Moxonidine



Plantes

- Réglisse (Rétention hydrique)
- Dong quai (Angelica sinensis), escine
  (Effet pro-arythmogène par allongement de QT)
- Ma huang (éphédrine), écorce de Yohimbe (Sympathicomimétique)
- Gossypol (Hypokaliémie)
- Pissenlit commun (Taraxacum officinale) Rétention hydro-sodée

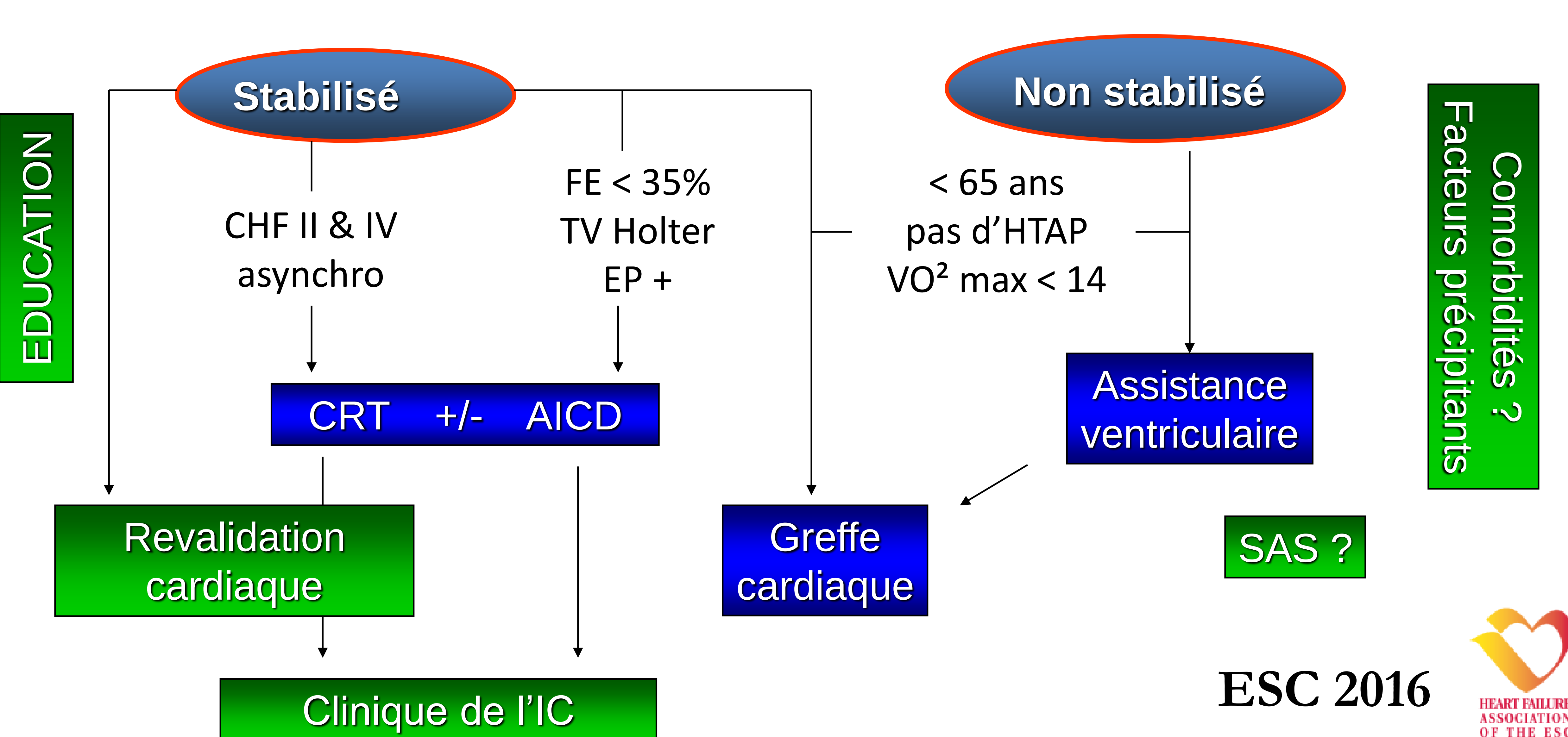
Recommendations	Class[a]	Level[b]	Ref[c]
Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	A	209, 210
NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	B	211–213
Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization.	III	C	214
The addition of an ARB (or renin inhibitor) to the combination of an ACE-I and an MRA is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalaemia.	III	C	

Et après les médicaments ???

L'approche
non médicamenteuse



Après le traitement médical maximal



Le problème





Problème des réhospitalisations précoces

Typical length of hospital stay is 5–10 days

EVEREST trial

Almost 1 out of 4 hospitalized patients (24%) are rehospitalized for heart failure within the **30-day post discharge period**[4]

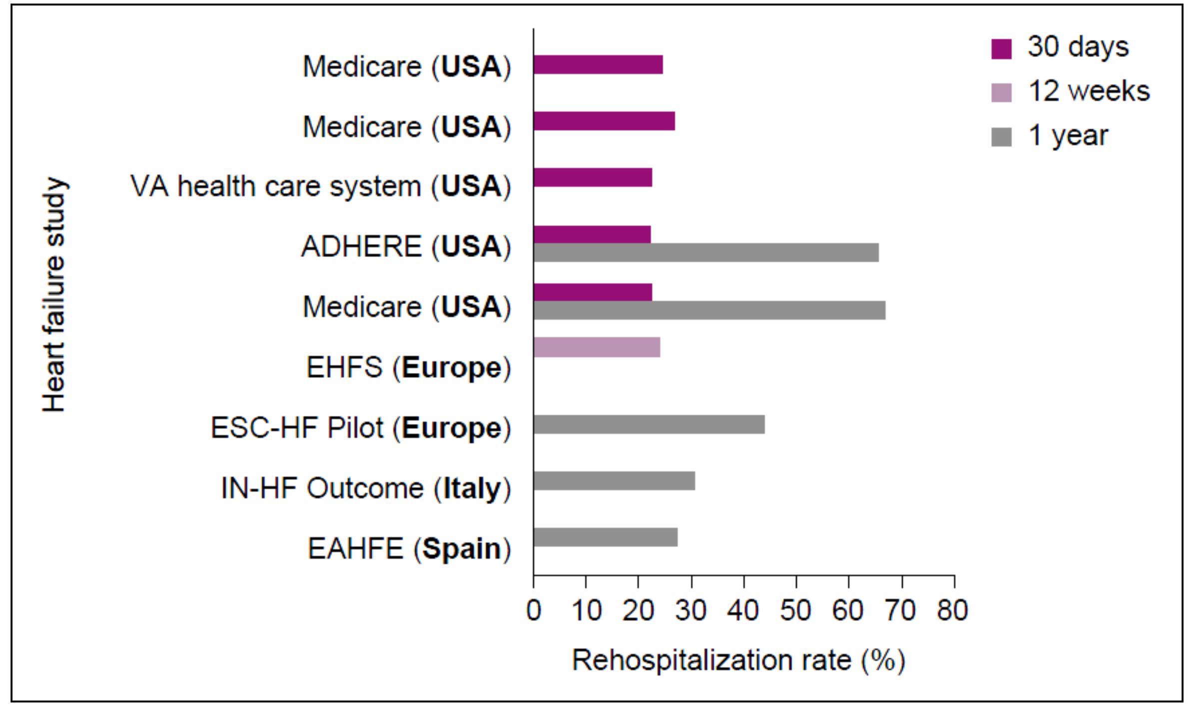
Nearly 1 out of 2 patients (46%) are rehospitalized for heart failure within the **60-day post discharge period**[4]

number of hospitalizations (0–1400)

	1-30 days	31-60 days	> 60 days
HF hospitalization	237 (24.1%)	191 (19.5%)	554 (56.4%)
Non-HF CV hospitalization	71 (19.5%)	74 (20.3%)	219 (60.2%)
Non-CV hospitalization	188 (23.1%)	148 (18.2%)	477 (58.7%)
Total	496 (23.0%)	413 (19.1%)	1250 (57.9%)

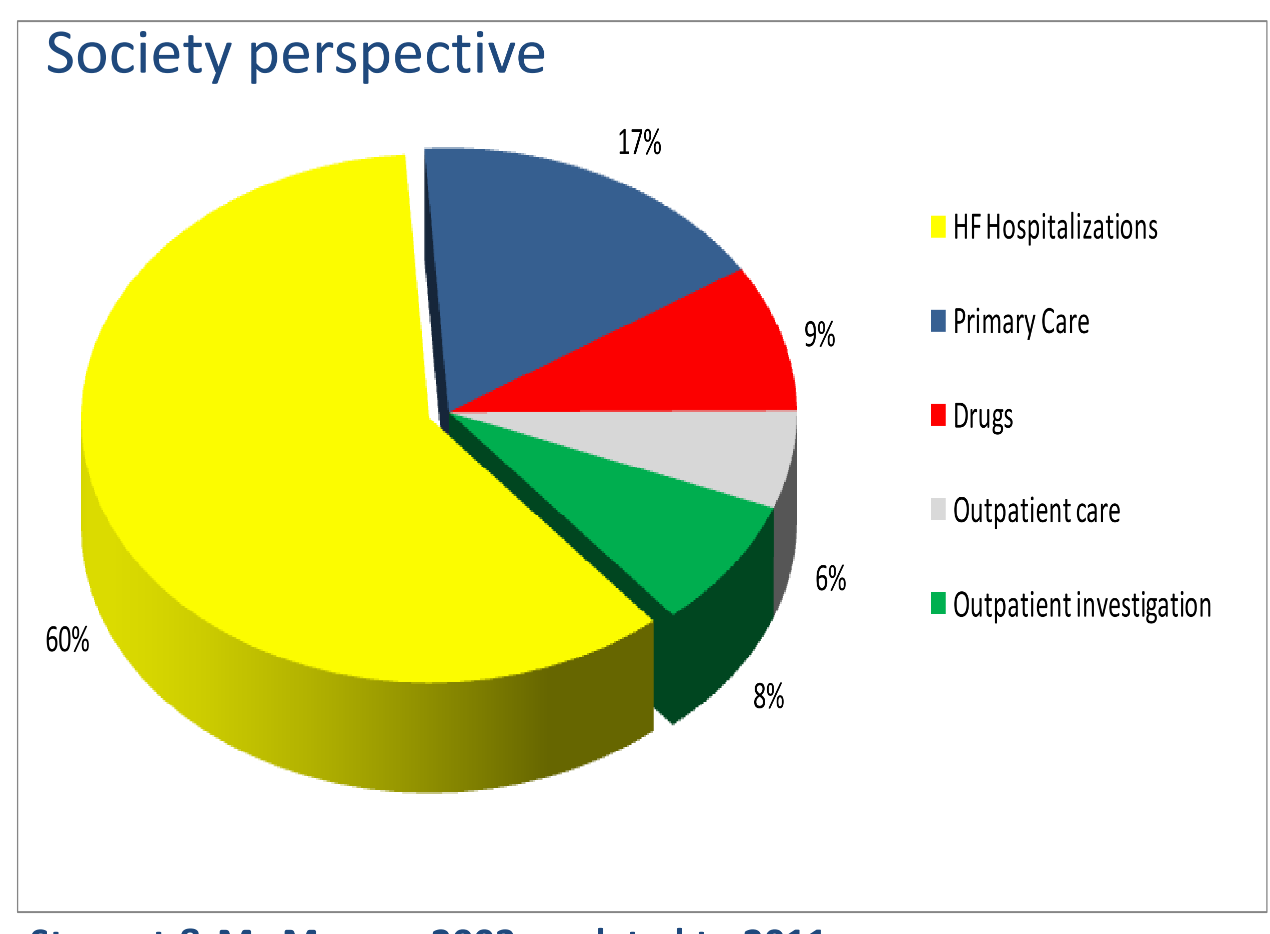
Timing of major causes of first hospitalization.

O'Connor CM, et al. *Am Heart J. 2010;159:841-849.*

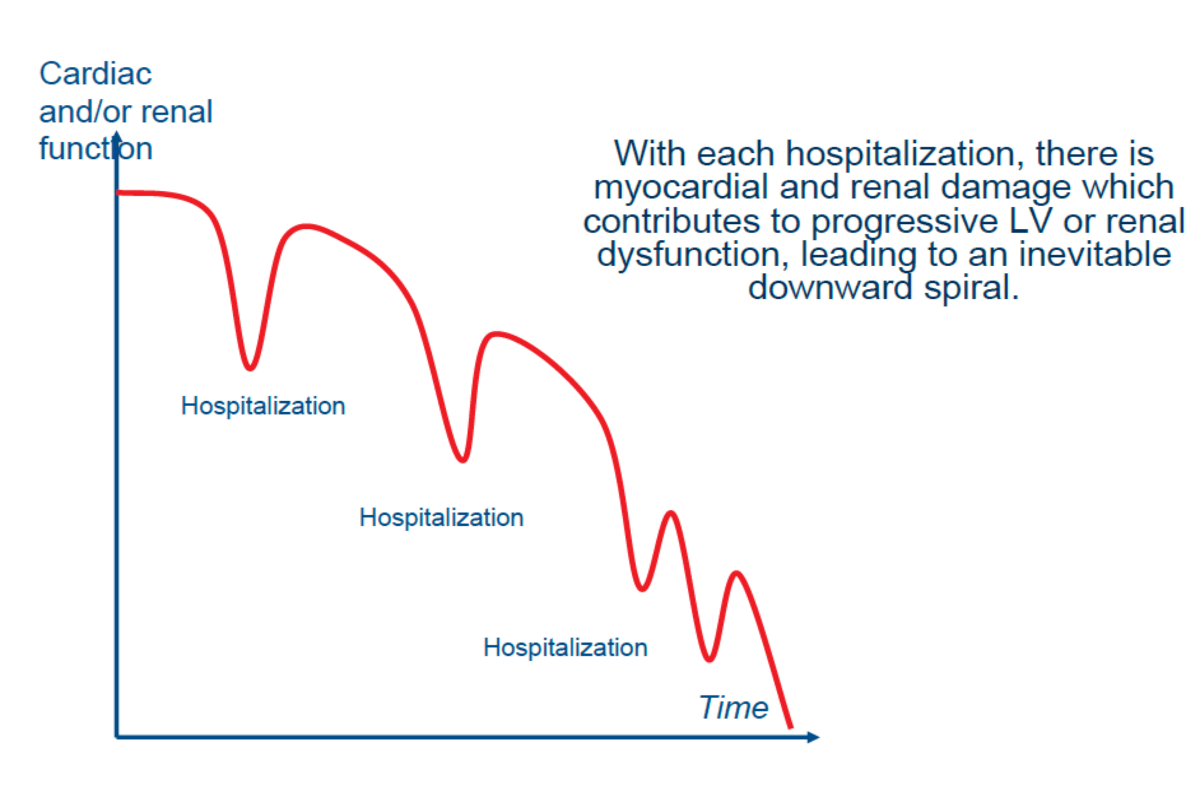


Martin R Cowie et al; Improving care for patients with acute heart failure, 2014

Problème des réhospitalisations
important pour diverses raisons



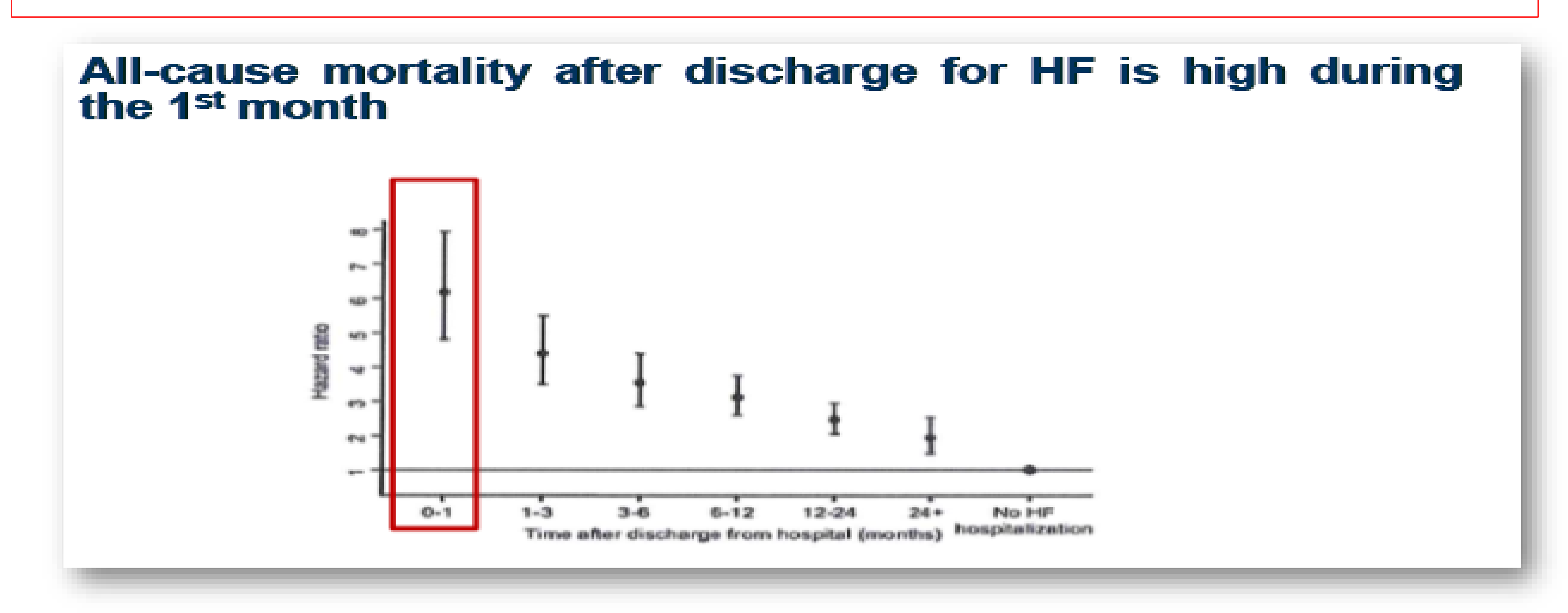
Stewart & Mc Murray, 2003, updated to 2011
British Heart Foundation, 2002 (updated to 2014)



Gheorghiade M, et al. *Am J Cardiol. 2005;96:11-17.*

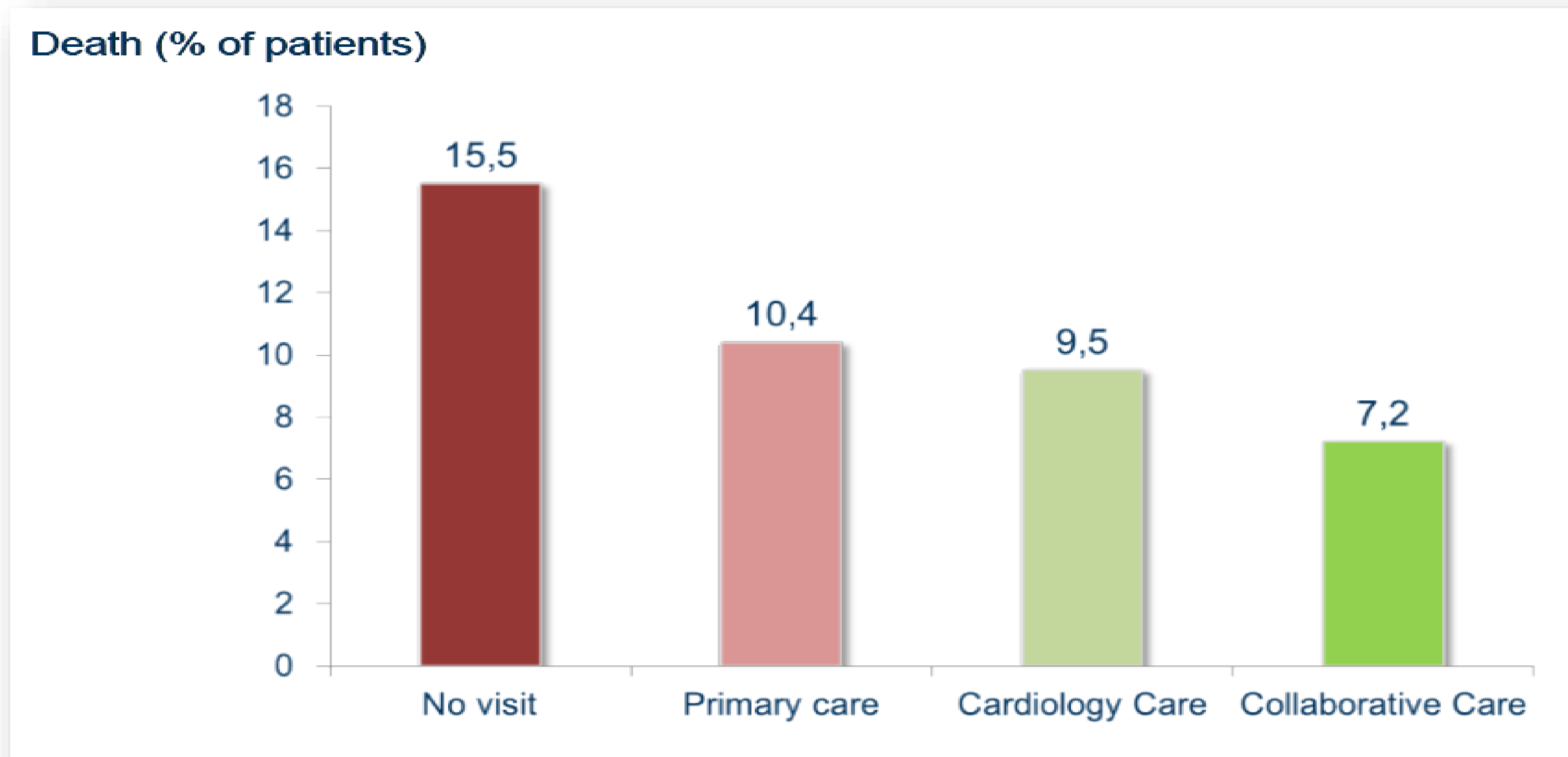
Hospitalizations account for most HF-associated costs
⇨ clear need to reduce hospitalizations!

LA MORTALITÉ EST PARTICULIÈREMENT ÉLEVÉE DANS LA PHASE PRÉCOCE APRÈS UNE HOSPITALISATION



Marti NC, et al. *Circ Heart Fail. 2013;6:1095-1101.*

En pratique, qui suit le patient après une hospitalisation ?



Actions pour réduire le taux de réadmissions

- **Impliquer** le patient et sa famille.
- **Réévaluation précoce** dans la semaine qui suit la sortie.
- **Collaboration** renforcée avec les médecins généralistes.
- Établir un **plan de suivi** (biologies, visites,…) et un **plan thérapeutique** pour **l’optimalisation du traitement** (titration IEC- BB).
- Mettre en place une **communication optimale** avec le médecin traitant.
- Inclure le patient dans un **programme pluri-disciplinaire**

McMurray J, et al. Eur Heart J. 2012;33:1787–847.
Bradley EH, et al. Circ Cardiovasc Qual Outcomes. 2013;6:444-450

Impliquer le patient dans sa prise en charge

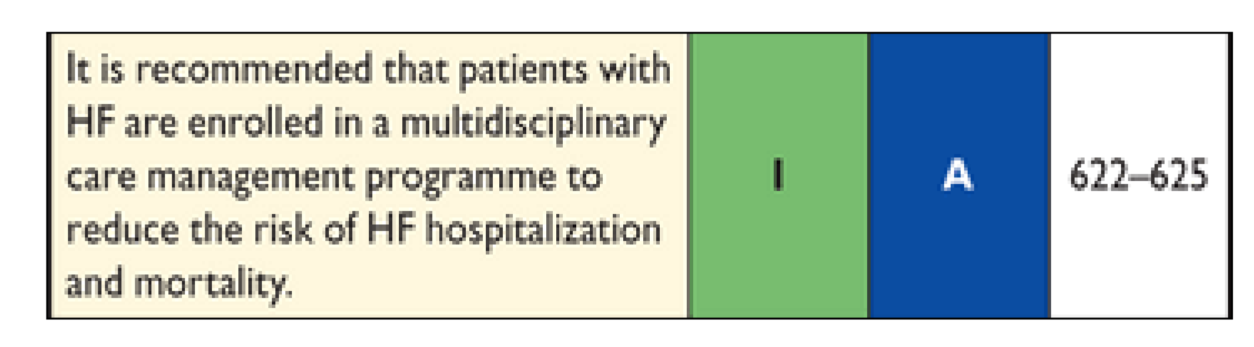
- ✓ Prendre en compte le **contexte** psycho-social et familial.
- ✓ Convenir d'**objectifs** partagés avec le patient et son entourage.
- ✓ Rappeler les **signes d'alerte** et la façon réagir de manière adaptée.
- ✓ Insister sur la mesure régulière du **poids**.
- ✓ Inclure le patient dans un **programme pluri-disciplinaire.**
- ✓ Mettre en garde contre **l'automédication** et les risques d'**interactions médicamenteuses.**

APPROCHE MULTIDISCIPLINAIRE
CLINIQUES DE L‘ INSUFFISANCE CARDIAQUE

Un système pluridisciplinaire coordonné pour la prise en charge de l’I.C.

- **améliore les symptômes (Classe I A)**
- **diminue les réhospitalisations (Classe I A)**
- **diminue la mortalité (Classe I A)**

Le modèle peut varier en fonction des ressources locales et de la population cible.



It is recommended that patients with HF are enrolled in a multidisciplinary care management programme to reduce the risk of HF hospitalization and mortality.	I	A	622–625



2016 ESC Guidelines for heart failure; European Heart Journal 20 May 2016,

Rôles & buts d'une clinique de l'IC



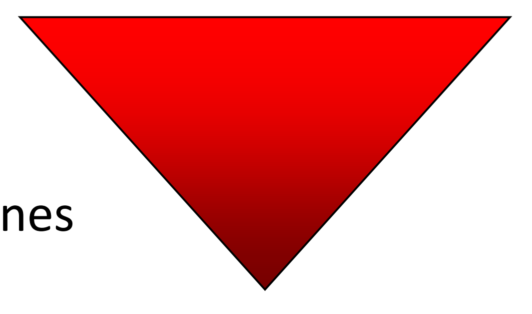
- Approche **pluri-disciplinaire coordonnée**
- Un centre **aisément accessible**
- Pour les patients à **haut risque**, symptomatiques
- **Informer et éduquer** les patients et leurs familles
- **Impliquer** le patient dans sa prise en charge
- Gérer la **transition hôpital – domicile**
- Établir un **plan thérapeutique complet** qui sera adapté (guidelines, CRT, Defib, EPO,…)
- Assurer un **suivi optimal** en **collaboration avec le MT**
- Gérer les **situations de crise et de détresse**
- **Soutien psychologique**

APPROCHE MULTIDISCIPLINAIRE

Partenaires

INFIRMIERE HFC

Information, éducation
Compréhension, compliance
Evaluer connaissances et acquis
Coordonner avec les autres disciplines
Contact téléphonique



CARDIOLOGUE

évaluation clinique
création d'un dossier
établir les objectifs &
protocole thérapeutique

MEDECIN TRAITANT

Veiller à l'application des recommandations à domicile
Adapter les objectifs au contexte psycho-social et familial
Suivi du Protocole thérapeutique et optimalisation
Poursuivre une éducation permanente au domicile

Prise en charge pluridisciplinaire
de l'Insuffisance cardiaque

Médecin Généraliste

Cardiologue

Psychologue

PATIENT
± sa famille

Diététicienne

Assistant social

Kinésithérapeute

Pharmacien

Infirmier au domicile

Infirmière éducatrice & Cardiologue
Coordinateurs du réseau

Éducation thérapeutique

ESC guidelines 2016

Les professionnels de la santé doivent informer, éduquer et conseiller de façon compréhensive les patients et leurs familles sur l’I.C.

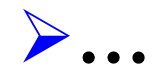
European Heart Jl (2016)

Différents outils existent mais…

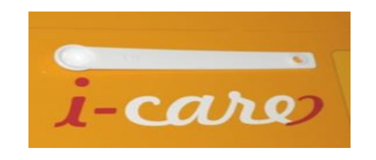




Éducation est limitée par

- **La fatigue du patient**
- **Son degré d’acceptation de la maladie**
- **La complexité des connaissances a assimilé**
-  **…**





Sujets éducationnels	Compétences et conduites adaptées
Définition et étiologie de l'IC	Comprendre les causes de l'IC et de survenue des symptômes
Symptômes et signes d'IC	Surveiller et reconnaître les signes et symptômes
	Se peser chaque jour et reconnaître une prise de poids rapide
	Savoir quand et comment contacter un soignant
	Prendre des diurétiques à la demande si pertinent et conseillé
Traitement pharmacologique	Comprendre les indications, les doses et les effets des médicaments
	Reconnaître les effets indésirables courants de chaque médicament prescrit
Modification des facteurs de risque	Comprendre l'importance de l'arrêt du tabac
	Surveiller la pression artérielle en cas d'HTA
	Obtenir un bon contrôle de la glycémie en cas de diabète
	Éviter l'obésité
Recommandations diététiques	Restriction sodée si prescrite
	Éviter un apport hydrique excessif
	Éviter l'alcool
	Surveiller et prévenir la malnutrition
Recommandations concernant l'activité physique	Vaincre les réticences à l'activité physique
	Comprendre les bénéfices de l'exercice
	Avoir un entraînement physique régulier
Activité sexuelle	Ne pas craindre les rapports sexuels et discuter des problèmes avec les professionnels de santé
	Comprendre les problèmes sexuels spécifiques et développer des stratégies permettant de les surmonter
Vaccination	Se faire vacciner contre la grippe et la pneumonie à pneumocoque
Troubles du sommeil et de la respiration	Adhérer à la prévention des FDR CVS tels que la perte de poids pour les obèses, l'arrêt du tabac et le sevrage d'alcool
	S'informer des options thérapeutiques si approprié
Observance	Comprendre l'importance du respect des recommandations thérapeutiques et d'une motivation soutenue à suivre le plan de soins
Aspects psychologiques	Comprendre que la dépression et les troubles cognitifs sont fréquents et que l'accompagnement social est important
	S'informer des options thérapeutiques si approprié
Pronostic	Comprendre l'importance des facteurs pronostiques et prendre des décisions réalistes
	Chercher un soutien psychosocial si approprié

REVALIDATION CARDIAQUE

ESC 2016 Guidelines

L’entraînement physique est bénéfique chez les patients insuffisants cardiaques.

(Classe I, Evidence: A)

- ➤Réduction des Hospitalisations pour IC
- ➤Régression des symptômes
- ➤Amélioration de la QoL &des capacités fonctionnelles.

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that regular aerobic exercise is encouraged in patients with HF to improve functional capacity and symptoms.	I	A	321, 618–621
It is recommended that regular aerobic exercise is encouraged in stable patients with HFrEF to reduce the risk of HF hospitalization.	I	A	618, 619







Pour Qui ? Indications



- Insuffisance cardiaque stable
- Classe fonctionnelle NYHA II et III
- Traitement médical optimalisé

Comment?

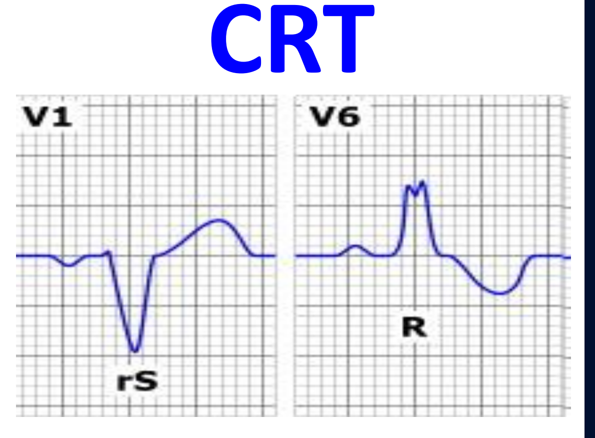
- Programme adapté et individualisé (intérêt ergospirométrie)
- Exercices progressifs (2 à 3 séances /semaines)
- Encadrement adéquat
- Programme long

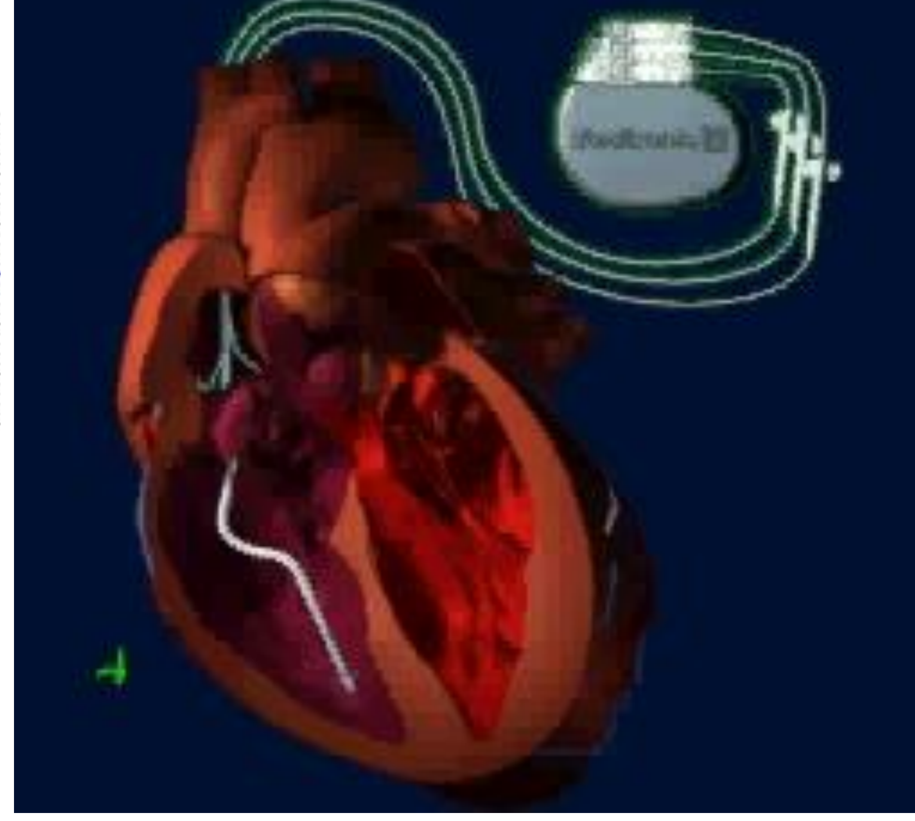


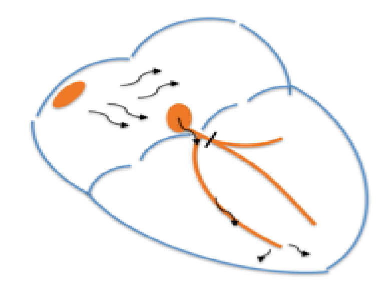
Evaluation des capacités fonctionnelles
Contrôle de la stabilité maladie

RESYNCHRONISATION
CRT





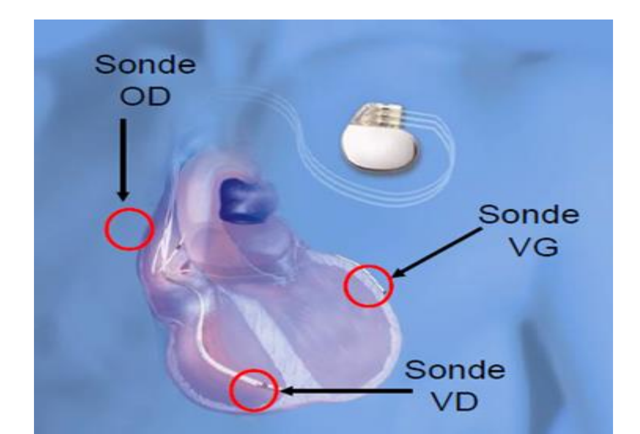


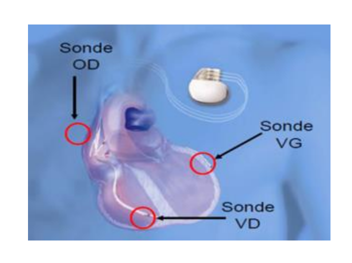


Patients sous traitement médical optimal

- **FE < 35 % ,**
- **NYHA II – IV**
- **QRS ≥ 130 ms,**

Certains patients asymptomatiques (FEVG < 35 %, QRS > 150 ms et RS)





Thérapie de Resynchronisation **CRT**

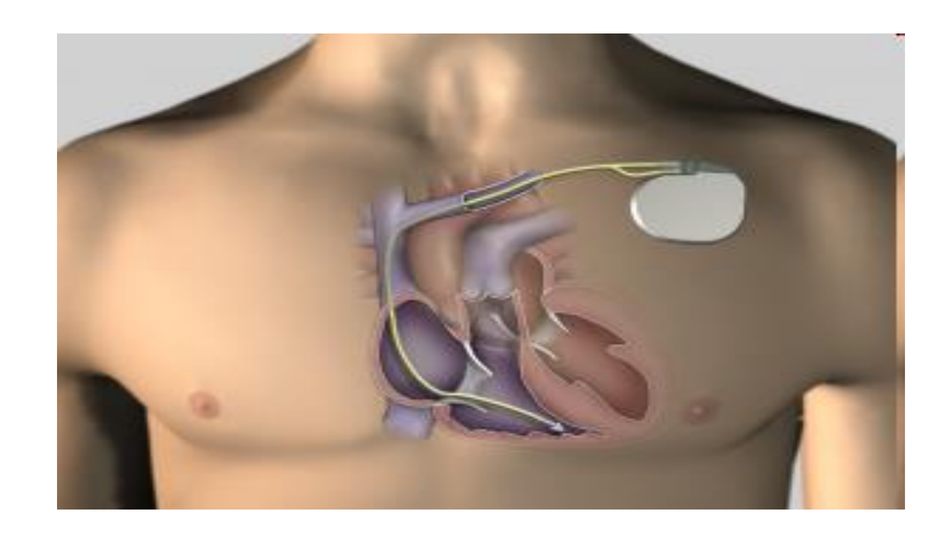
Recommendations	Class[a]	Level[b]	Ref[c]
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	A	261–272
CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIa	B	261–272
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	B	266, 273
CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIb	B	266, 273
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1).	I	A	274–277
CRT should be considered for patients with LVEF ≤35% in NYHA Class III–IV[d] despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥130 msec provided a strategy to ensure bi-ventricular capture is in place or the patient is expected to return to sinus rhythm.	IIa	B	275, 278–281
Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF.	IIb	B	282
CRT is contra-indicated in patients with a QRS duration < 130 msec.	III	A	266, 283–285

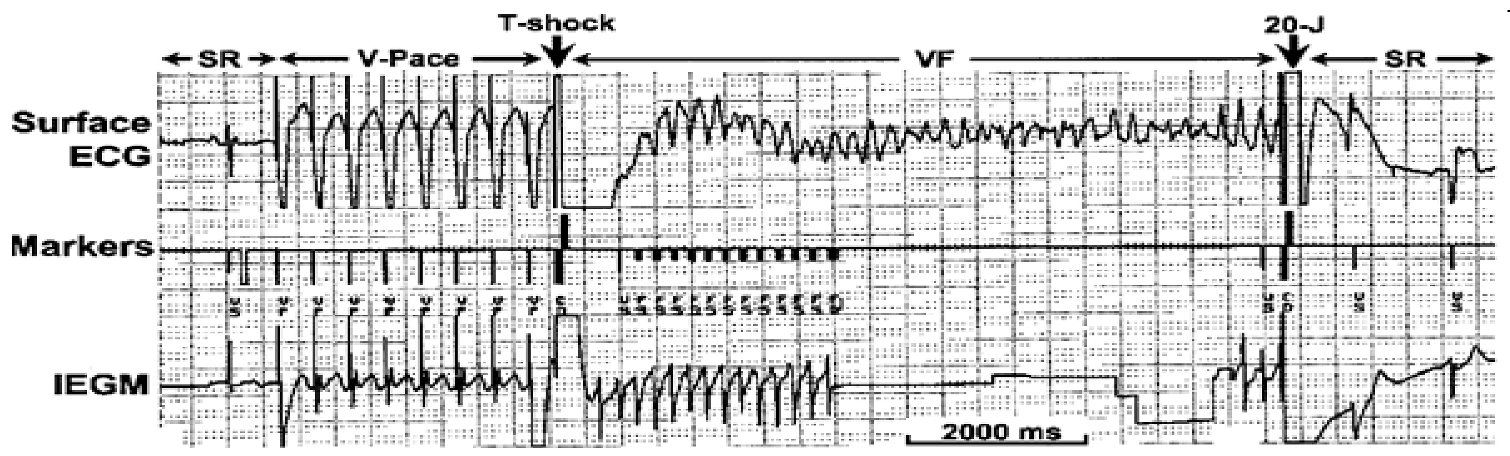


2016 ESC Guidelines for heart failure;
European Heart Journal 20 May 2016,

Le défibrillateur implantable
ICD - AICD







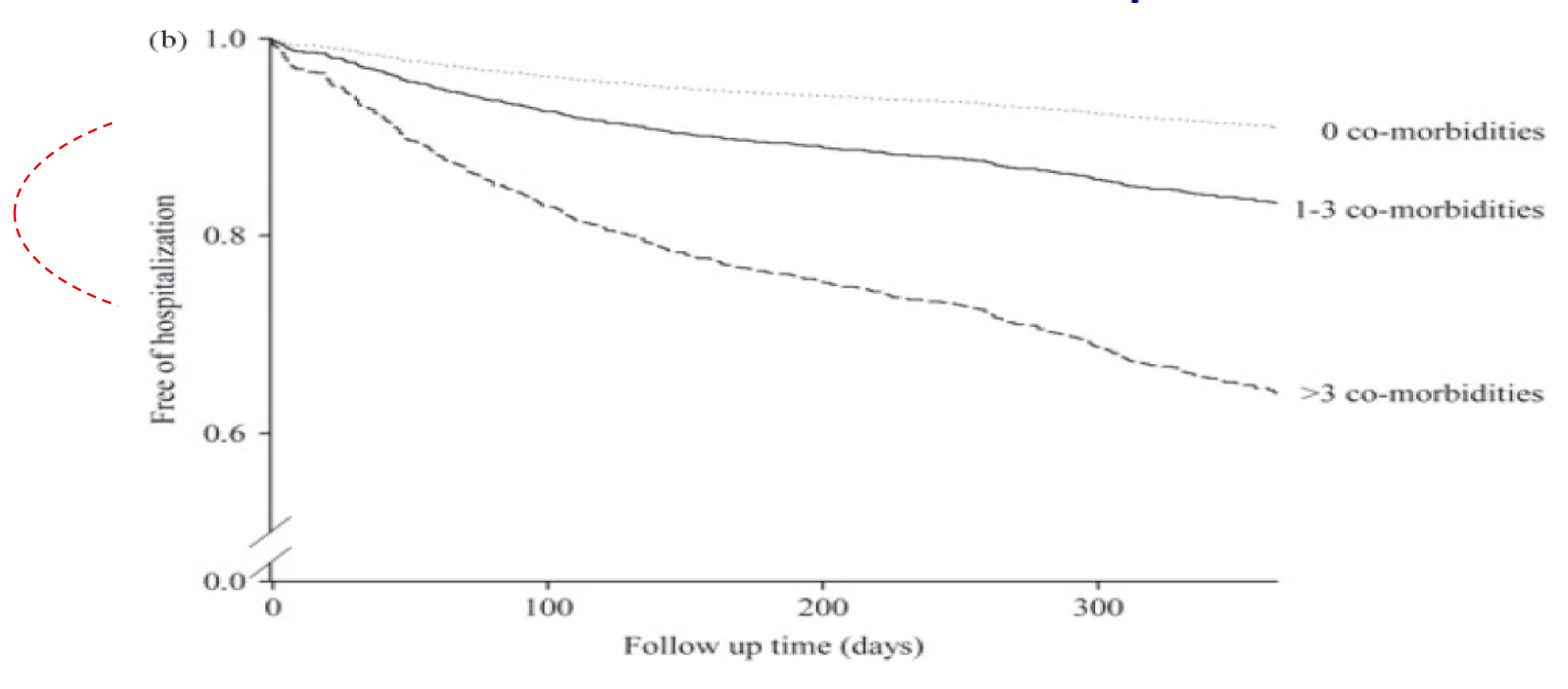
Le défibrillateur implantable
ICD - AICD

Recommendations	Class[a]	Level[b]
Secondary prevention An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status.	I	A
Primary prevention An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II–III), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than one year with good functional status, and they have:		
• IHD (unless they have had an MI in the prior 40 days – see below).	I	A
• DCM.	I	B
ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis.	III	A
ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a ventricular assist device, or cardiac transplantation.	III	C
Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals and the patient's needs and clinical status may have changed.	IIa	B
A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to an implanted device.	IIb	C

Patients with a QRS duration ≥130 ms should be considered for a defibrillator with CRT (CRT-D) rather than ICD.

Les comorbidités

Co-morbidities and HF-hospitalization



Van Deursen VM, et al. *EJHF*. 2014.

Les comorbidités

- CAD / ischemia & Hypertension
- Diabetes mellitus & Metabolic syndrome
- Sleep apnea
- COPD
- Depression / other neurological disease
- Liver & bowel dysfunction
- Renal dysfunction and kidney injury
- Anemia and iron deficiency
- Cachexia & muscle wasting

1. interfere with the diagnostic process of HF (e.g. COPD as a potentially confounding cause of dyspnoea).[390, 391]
2. aggravate HF symptoms and further impair quality of life.[391, 392]
3. contribute to the burden of hospitalizations and mortality,[393] as the main cause of readmissions at 1 and 3 months.[394]
4. may affect the use of treatments for HF (e.g. renin–angiotensin system inhibitors contra-indicated in some patients with severe renal dysfunction or beta-blockers relatively contra-indicated in asthma).[395, 396]
5. evidence base for HF treatment is more limited as co-morbidities were mostly an exclusion criterion in trials; efficacy and safety of interventions is therefore often lacking in the presence of co-morbidities.
6. drugs used to treat co-morbidities may cause worsening HF (e.g. NSAIDs given for arthritis, some anti-cancer drugs).[397]
7. interaction between drugs used to treat HF and those used to treat co-morbidities, resulting in lower efficacy, poorer safety, and the occurrence of side effects (e.g. beta-blockers for HFrEF and beta-agonists for COPD and asthma).[391, 395, 396]

IC & HTA

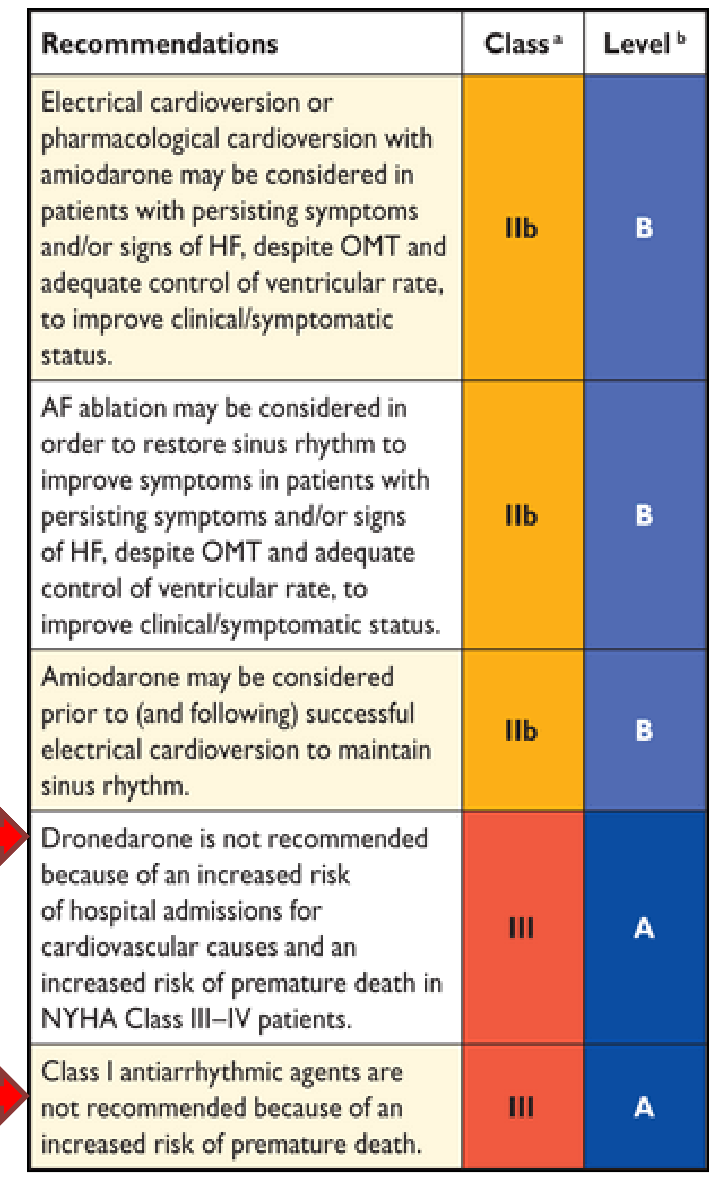
Recommendations	Class[a]	Level[b]
Step 1		
ACE-I (or ARB), a beta-blocker or an MRA (or a combination) is recommended to reduce blood pressure as first-, second- and third-line therapy, respectively, because of their associated benefits in HFrEF (reducing the risk of death and HF hospitalization). They are also safe in HFpEF.	I	A
Step 2		
A thiazide diuretic (or if the patient is being treated with a thiazide diuretic, switching to a loop diuretic) is recommended to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together withan ACE-I), a beta-blocker and an MRA.	I	C
Step 3		
Amlodipine or hydralazine is recommended to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together withan ACE-I), a beta-blocker, an MRA and a diuretic.	I	A
Felodipine should be considered to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together withan ACE-I), a beta-blocker, an MRA and a diuretic.	IIa	B
Moxonidine is not recommended to reduce blood pressure because of safety concerns in HFrEF patients (increased mortality).	III	B
Alpha-adrenoceptor antagonists are not recommended to reduce blood pressure because of safety concerns in HFrEF patients (neurohormonal activation, fluid retention, worsening HF).	III	A
Diltiazem and verapamil are not recommended to reduce blood pressure in patients with HFrEF because of their negative inotropic action and risk of worsening HF.	III	C



2016 ESC Guidelines for heart failure; European Heart Journal 20 May 2016,

Fibrillation Auriculaire

Recommendations	Class [a]	Level [b]
The CHA_2DS_2-VASc and HAS-BLED scores are recommended tools in patients with HF for the estimation of the risk of thromboembolism and the risk of bleeding associated with oral anticoagulation, respectively.	I	B
An oral anticoagulant is recommended to prevent thrombo-embolism for all patients with paroxysmal or persistent/permanent AF and a CHA_2DS_2-VASc score ≥2, without contra-indications, and irrespective of whether a rate or rhythm management strategy is used (including after successful cardioversion).	I	A
NOAC treatment is contra-indicated in patients with mechanical valves or at least moderate mitral stenosis.	III	B
In patients with AF of ≥48 h duration, or when the duration of AF is unknown, an oral anticoagulant is recommended at a therapeutic dose for ≥3 weeks prior to electrical or pharmacological cardioversion.	I	B
Intravenous heparin or LMWH and TOE quided strategy is recommended for patients who have not been treated with an anticoagulant dose for ≥3 weeks and require urgent electrical or pharmacological cardioversion for a life threatening arrhythmia.	I	C
Combination of an oral anticoagulant and an antiplatelet agent is not recommended in patients with chronic (>12 months after an acute event) coronary or other arterial disease, because of a high-risk of serious bleeding. Single therapy with an oral anticoagulant is preferred after 12 months.	III	C
For patients with HF and non-valvular AF eligible for anticoagulation based on a CHA_2DS_2-VASc score, NOACs rather than warfarin should be considered for anticoagulation as NOACs are associated with a lower risk of stroke, intracranial haemorrhage and mortality, which outweigh the increased risk of gastrointestinal haemorrhage.	IIa	B



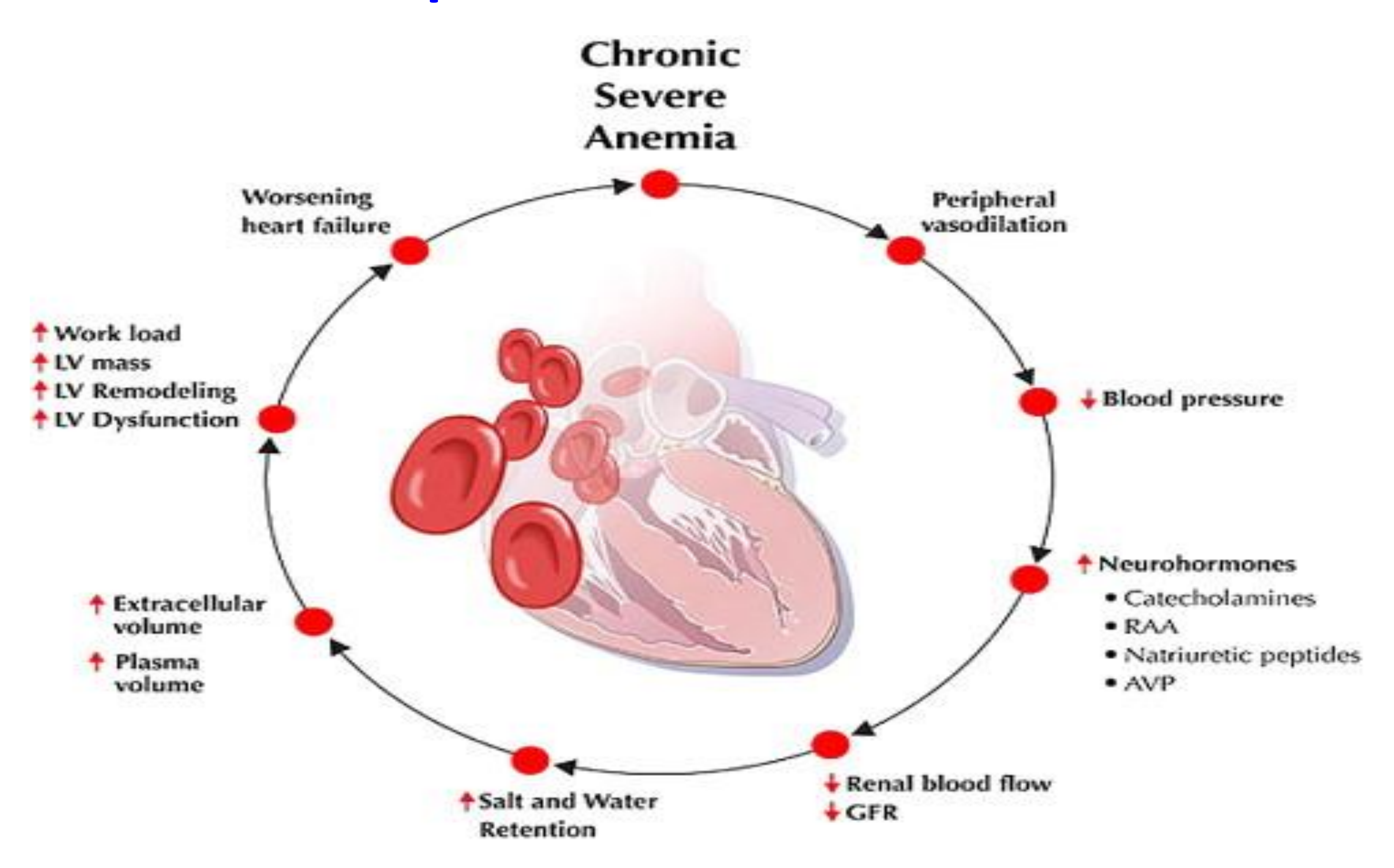
Recommendations	Class [a]	Level [b]
Electrical cardioversion or pharmacological cardioversion with amiodarone may be considered in patients with persisting symptoms and/or signs of HF, despite OMT and adequate control of ventricular rate, to improve clinical/symptomatic status.	IIb	B
AF ablation may be considered in order to restore sinus rhythm to improve symptoms in patients with persisting symptoms and/or signs of HF, despite OMT and adequate control of ventricular rate, to improve clinical/symptomatic status.	IIb	B
Amiodarone may be considered prior to (and following) successful electrical cardioversion to maintain sinus rhythm.	IIb	B
Dronedarone is not recommended because of an increased risk of hospital admissions for cardiovascular causes and an increased risk of premature death in NYHA Class III–IV patients.	III	A
Class I antiarrhythmic agents are not recommended because of an increased risk of premature death.	III	A

« **En dessous de 0,5 ng/mL** de digoxine vous n'êtes pas efficace,
au-dessus d'1,2 ng/mL, vous êtes dangereux », rappelait le **Pr Cohen-Solal**

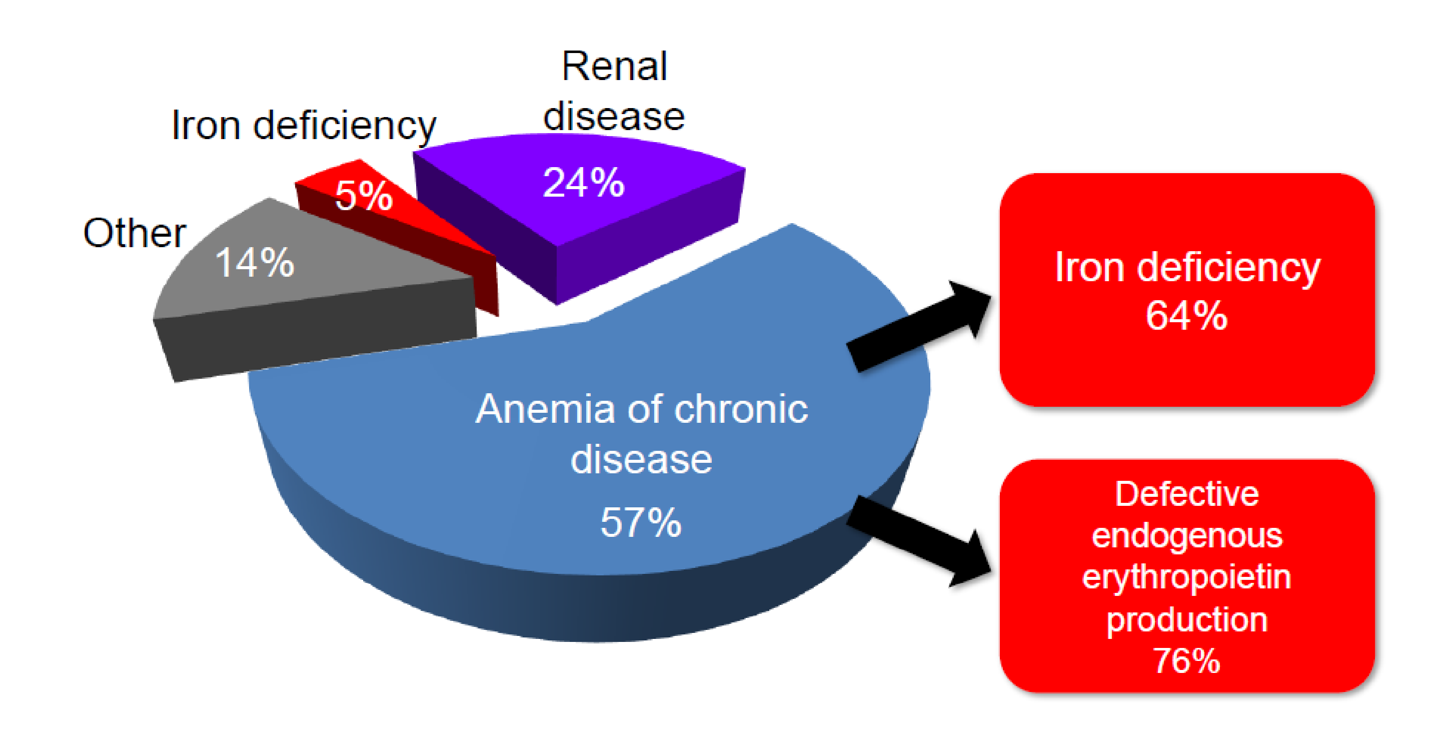


2016 ESC Guidelines for heart failure;
European Heart Journal 20 May 2016,

Conséquences de l'anémie dans l'IC



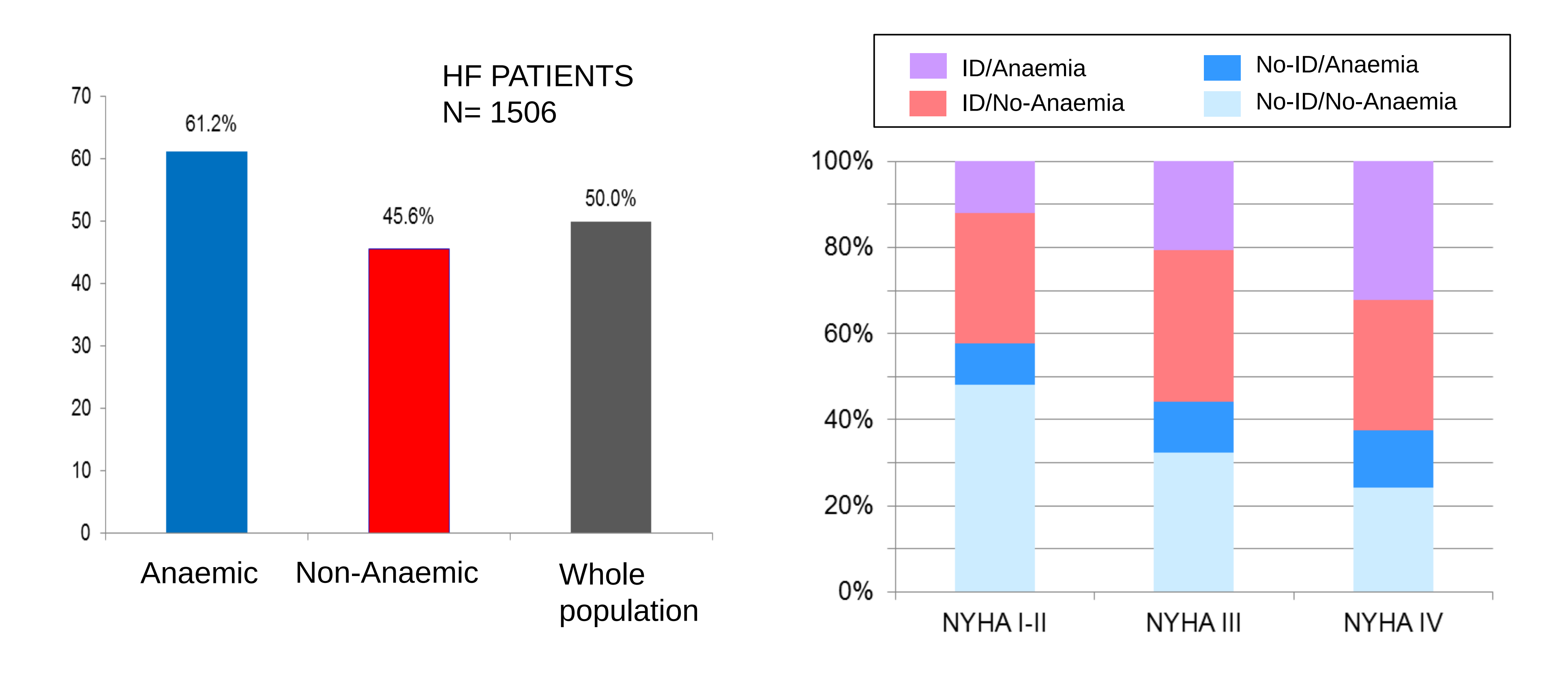
La Carence martiale est la principale cause d'anémie dans l'IC



N=148 anemic CHF patients

Opasich C, et al. Eur Heart J 2005;26:2232–7.

La Carence martiale est fréquente dans l'IC



"Disease severity, assessed by NYHA class and NT-proBNP levels, proved to be powerful and independent predictors of a disordered iron status"

Iron deficiency definition used:

− Serum ferritin <100 µg/L or

− Serum ferritin 100-299 µg/L with TSAT <20%

Klip IT, et al. *Am Heart J* 2013;165:575-82.

Causes de la Carence martiale dans l'IC

Malnutrition

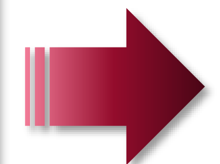
- Loss of appetite: <50% intake

Malabsorption:

- GI oedema
- PPI, PO_4 binders (calcium based)

GI blood losses

- Anti-platelets
- Anti-coagulants
- NSAIDs
- Mucosal integrity

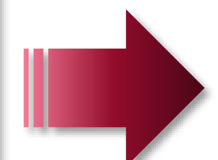


Réserves de fer épuisées: Carence en fer absolue

Inflammation

Cytokines, IL-6, IL-1, TNF-α

- Blunted responses to EPO
- Apoptosis of erythroid progenitors
- Hepcidin-mediated malabsorption and RES pooling

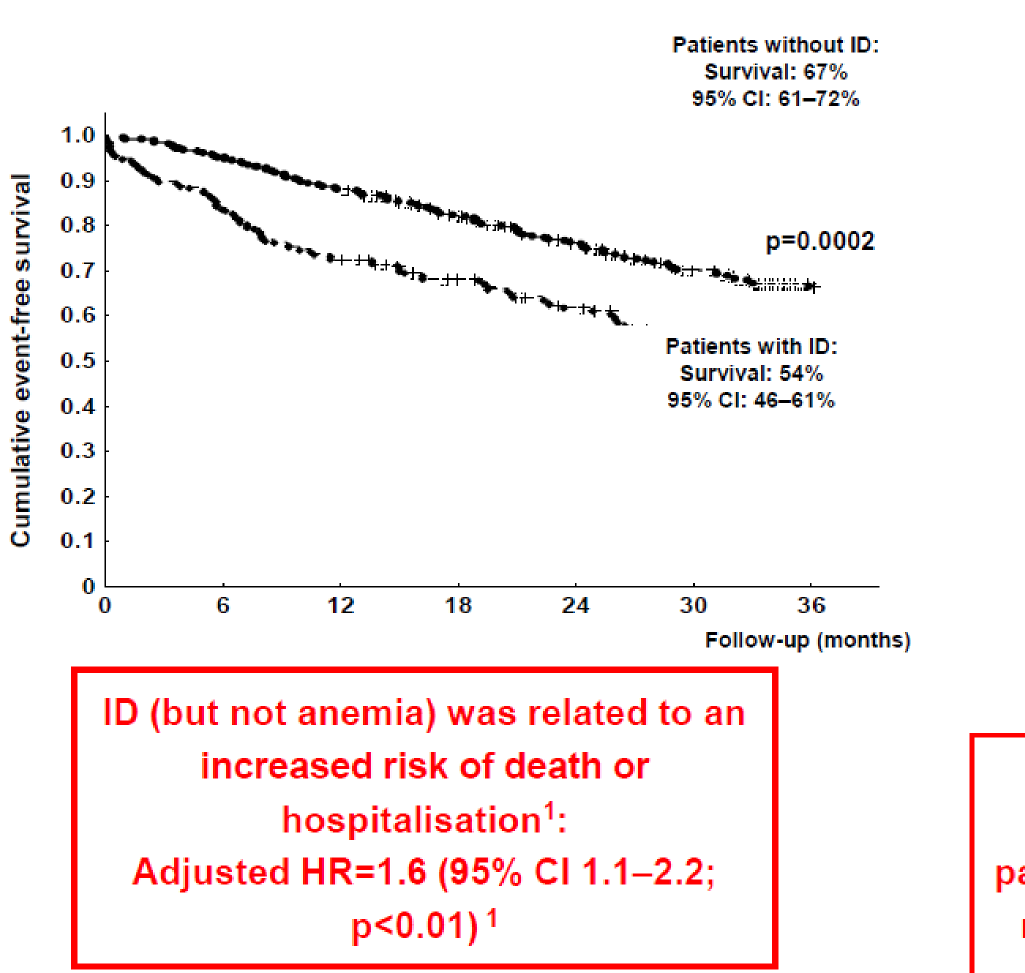


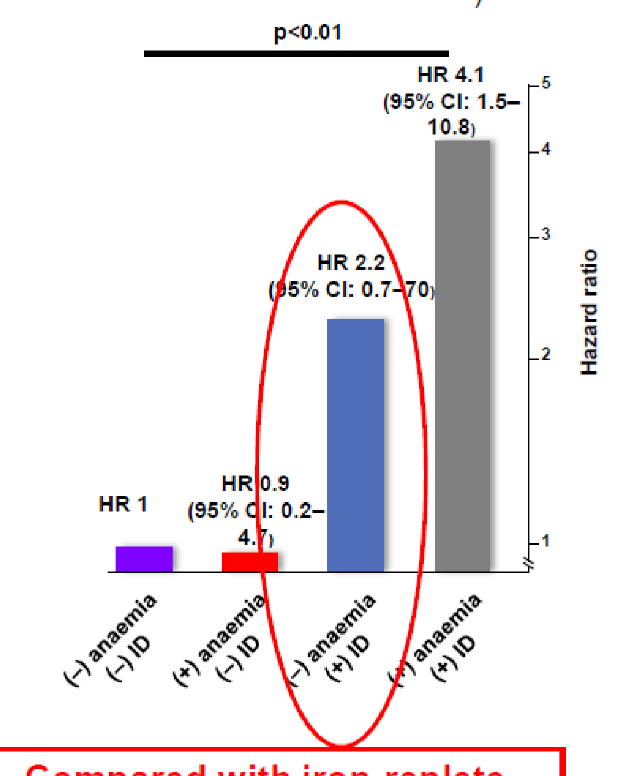
Disponibilité insuffisante des réserves de fer : Carence en fer fonctionnelle

Jankowska EA, et al. *Eur. Heart J* 2013;34:816-29.

La carence en fer est associée à une augmentation de la morbidité et de la mortalité également en absence d'anémie

Iron deficiency: Ferritin <100 mg/L, or 100–300 mg/L with transferrin saturation <20%)



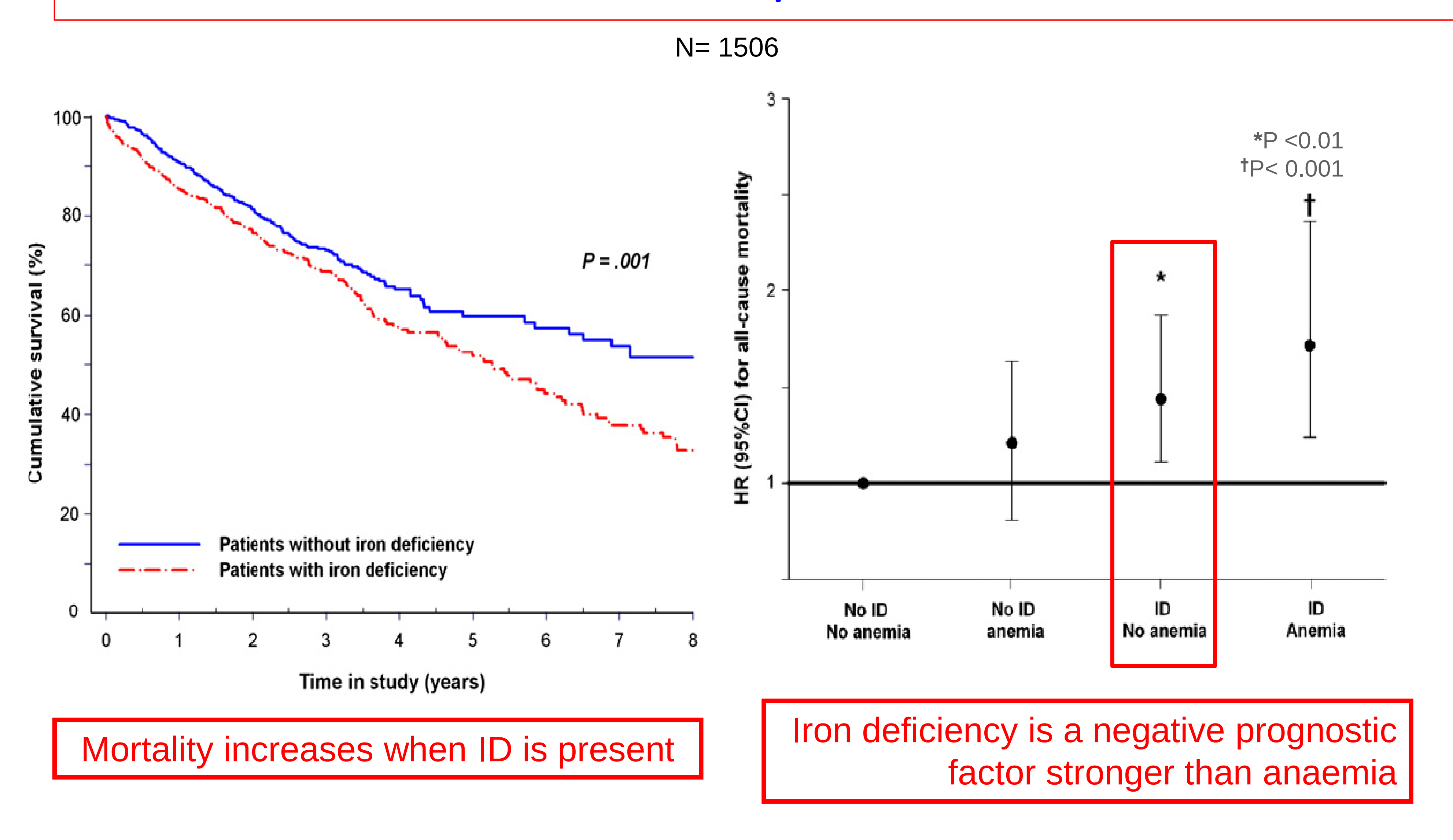


ID (but not anemia) was related to an increased risk of death or hospitalisation[1]: Adjusted HR=1.6 (95% CI 1.1–2.2; p<0.01) [1]

Compared with iron-replete patients without anemia, ID patients had 2–4-fold escalated risk for death irrespective of anemic status[2]

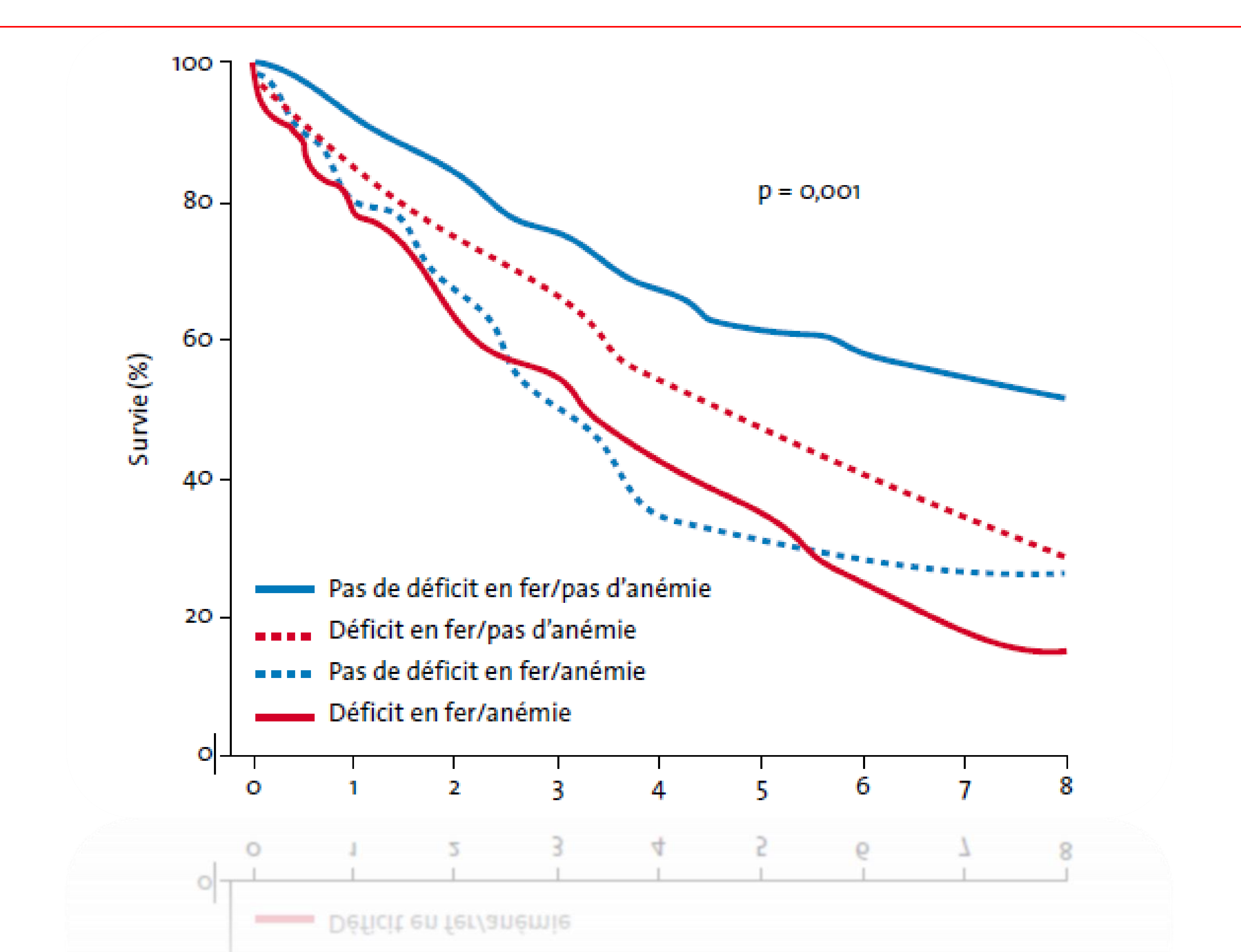
1. Jankowska EA et al: Eur Heart J 2010
2. Okonko DO, et al. J Am Coll Cardiol 2011;58:1241–51

La carence en fer mais pas l'anémie est associée à un faible résultat chez les patients atteints de CHF



Klip IT, et al. *Am Heart J* 2013;165:575-82.

Facteur pronostique indépendant de décès



Effets néfastes de la carence martiale sur le plan clinique et sur le plan cellulaire

VE/VCO_2 ↑

VO_2 max ↓

Tolérance à l'effort ↓

Hospitalisations ↑

Mortalité ↑

CARENCE MARTIALE

Capacité O_2 ↓ (= myoglobine)

Remodelage ↑

Transport de l'O_2 ↓ (= hémoglobine)

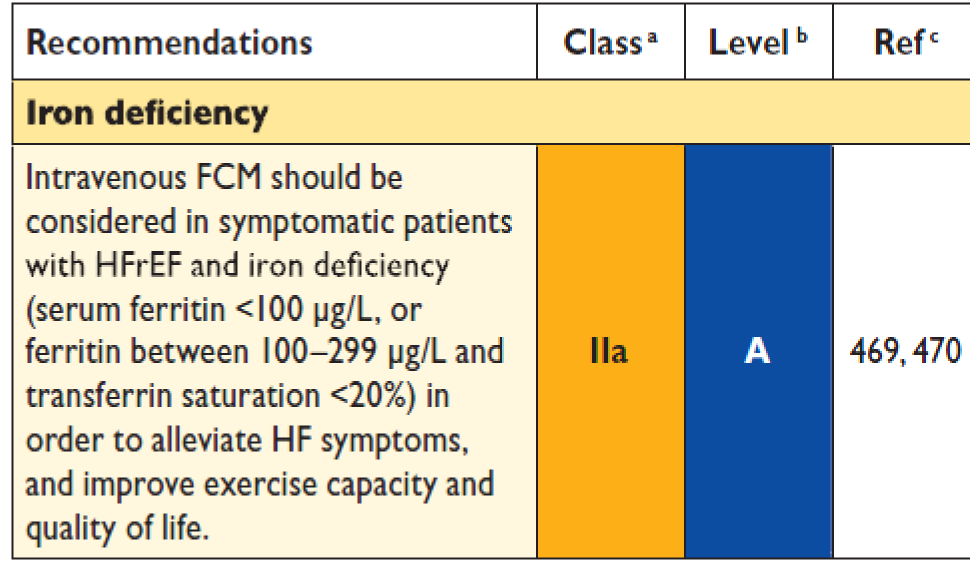
Activation neurohormonale ↑

Métabolisme oxydatif ↓

Dysfonction mitochondriale

Manque de molécules énergétiques (p. ex. ATP,...)

Métabolisme anaérobie ↑



Recommendations	Class [a]	Level [b]	Ref [c]
Iron deficiency			
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	IIa	A	469, 470

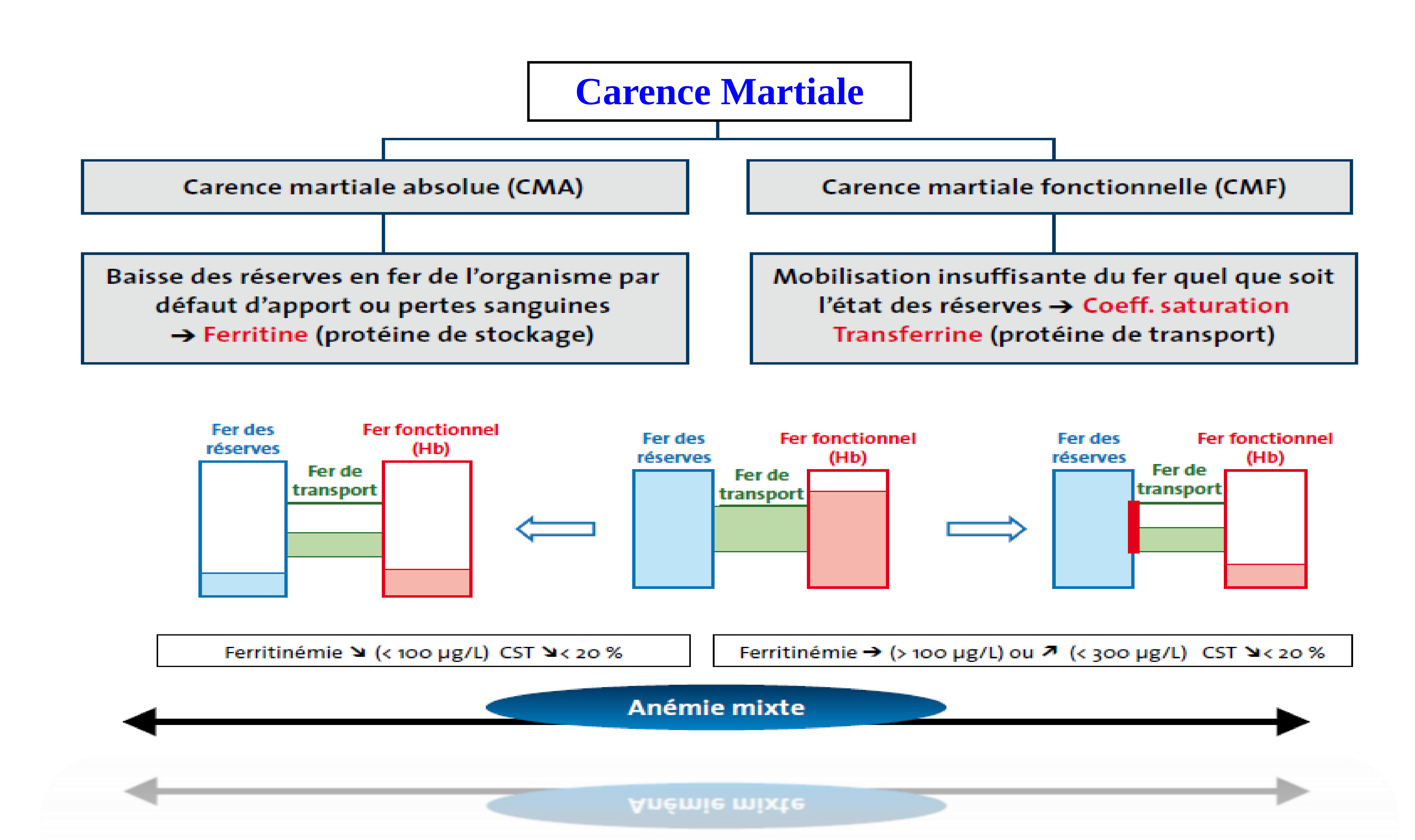
P. Martens & W. Mullens; JDC 28, N° 1, FÉVRIER 2016

Diagnostic de la carence en fer

Paramètres	Pertinence pour le diagnostic du fer
Hémoglobine (Hb) - g/dl	La valeur de l'hémoglobine est une mesure pour l'anémie, pas pour la carence en fer
Ferritine sérique - µg/l (attention inflammation)	Fournit des informations sur les réserves de fer
Saturation de la transferrine - % (Formule : Fer sérique/TIBC [*Total iron binding capacity*])	Information sur le fer transporté (lié à la transferrine)
CRP (protéine C réactive) (mg/l)	Marqueur d'inflammation

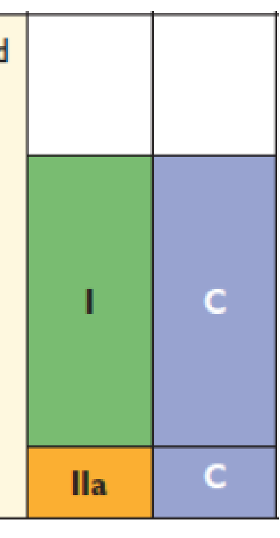
Fer sérique - µmol/l	Moins utilisable pour déterminer une carence en fer

Raymakers, Kreutzer & Schneeberger, 2006


Carence Martiale
Carence martiale absolue (CMA)
Carence martiale fonctionnelle (CMF)
Baisse des réserves en fer de l'organisme par défaut d'apport ou pertes sanguines
→ Ferritine (protéine de stockage)
Mobilisation insuffisante du fer quel que soit l'état des réserves → Coeff. saturation Transferrine (protéine de transport)
Fer des réserves
Fer de transport
Fer fonctionnel (Hb)
Fer des réserves
Fer de transport
Fer fonctionnel (Hb)
Fer des réserves
Fer de transport
Fer fonctionnel (Hb)
Ferritinémie ↘ (< 100 µg/L) CST ↘ < 20 %
Ferritinémie → (> 100 µg/L) ou ↗ (< 300 µg/L) CST ↘ < 20 %
Anémie mixte

Approche diagnostique chez les patients avec IC

Biologie Sanguine



The following diagnostic tests are recommended/should be considered for initial assessment of a patient with newly diagnosed HF in order to evaluate the patient's suitability for particular therapies, to detect reversible/treatable causes of HF and co-morbidities interfering with HF:		
- haemoglobin and WBC - sodium, potassium, urea, creatinine (with estimated GFR) - liver function tests (bilirubin, AST, ALT, GGTP) - glucose, HbA1c - lipid profile - TSH - ferritin, TSAT = TIBC	I	C
- natriuretic peptides	IIa	C





2016 ESC Guidelines for heart failure; European Heart Journal 20 May 2016,

Traitement
de la carence en fer & de l'anémie ferriprive

- Fer par voie orale (carence martiale/anémie)
- Fer par voie IV (carence martiale/anémie)
- EPO (seulement en cas d'anémie)
- Transfusion sanguine (seulement en cas d'anémie)

L'administration de fer intramusculaire est obsolète[1]

Dignass - Gassche et al 2015 - ECCO guideline on IDA in IBD

Intravenous Iron in CHF: Early Clinical Evidence

Authors	N	Design	Inclusion	Regimen and total iron dose	Follow-up (months)	Key results
Bolger[1] 2006	16	Open, no control	Hb ≤12 g/dL Serum ferritin ≤400 ng/mL	Iron sucrose, maximum 1000 mg iron i.v. (200 mg iron days 1, 3 and 5, plus days 15 and 17 if serum ferritin <400 ng/mL on day 12)	3	↑Hb ↑HRQoL ↑Exercise capacity (6MWT)
Toblli[2] 2007	40	Double-blind, randomized, placebo- controlled	Hb <12.5 g/dL for men; <11.5 g/dL for women Serum ferritin <100 ng/mL and/or TSAT ≤20%	Iron sucrose, 200 mg iron i.v. weekly for 5 weeks (total 1000 mg iron)	6	↑Hb ↑HRQoL ↑Exercise capacity (6MWT) ↑LVEF ↓NYHA ↑Renal function (↓NT-proBNP level)
Okonko[3] 2008	35	Single-blind, randomized, controlled	Hb <12.5 g/dL (anaemic group); 12.5–14.5 g/dL (non-anaemic group) Serum ferritin <100 ng/mL or 100–300 ng/mL with TSAT <20%	Iron sucrose, 200 mg iron i.v. weekly until serum ferritin ≥500 ng/mL, then 200 mg iron every 4 weeks to week 16. Required iron dose calculated using Ganzoni formula	4	↓HF symptoms (PGA) ↑Exercise tolerance (peak VO_2) ↓NYHA ↓Fatigue score
Usmanov[4]	32	Open, no control	Hb <11 g/dL Serum ferritin not specified	Iron sucrose, 100 mg iron i.v. three times weekly for 3 weeks, then once weekly for 23 weeks (total 3200 mg iron)	6	↓NYHA (in NYHA class III patients) ↑Echocardiographic indices

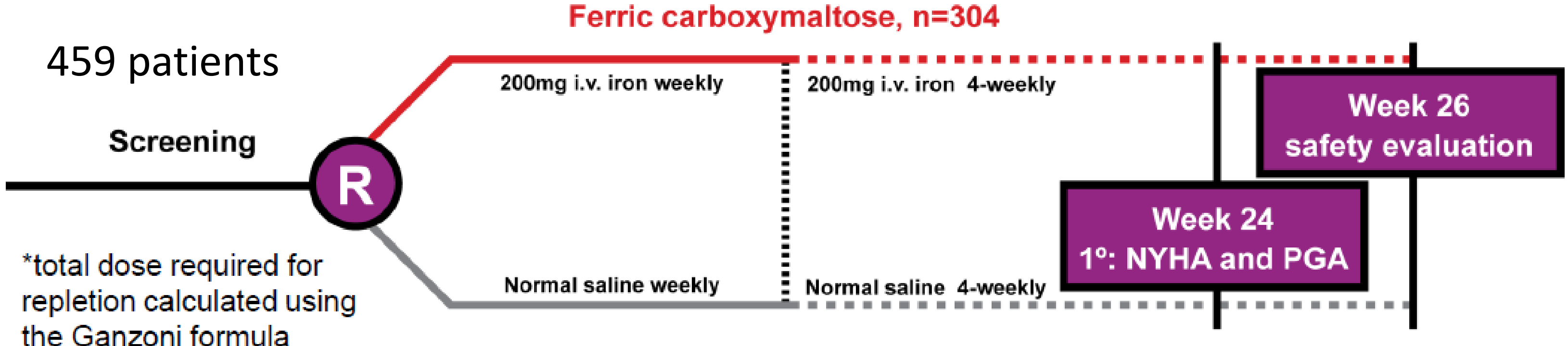
1. Bolger et al. *J Am Coll Cardiol* 2006;48:1225–7
2. Toblli et al. *J American Coll Cardiol* 2007;50:1657–65
3. Okonko et al. *J Am Coll Cardiol* 2008;51:103–12
4. Usmanov et al. *J Nephrol* 2008;21:236–42



FAIR-HF - Study Design

- **Main inclusion criteria:**
  - NYHA class II / III, LVEF ≤40% (NYHA II) or ≤45% (NYHA III)
  - Hb: 9.5–13.5g/dL
  - **Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%**
- **Treatment adjustment algorithm:**
  - Interruption: Hb>16.0g/dL or ferritin>800µg/L or ferritin>500µg/L, if TSAT>50%
  - Restart: Hb <16.0g/dL and serum ferritin <400µg/L and TSAT<45%
- **Blinding:**
  - Clinical staff: unblinded and blinded personnel
  - Patients: usage of curtains and black syringes for injections





*total dose required for repletion calculated using the Ganzoni formula

Anker *et al*, *Eur J Heart Failure* 2009;11:1084-1091



NYHA, PGA, QoL, 6min-Walking-Test
Week 4, 12 & 24

Patient Global Assessment

P<0.001 P<0.001 P<0.001

Odds ratio (95% confidence interval)

Favours FCM

Favours Placebo

Weeks after randomization

NYHA functional class

P<0.001 P<0.001 P<0.001

Odds ratio (95% confidence interval)

Favours FCM

Favours Placebo

Weeks after randomization

2 co-primary endpoints

6-minute walk test

P<0.001 P<0.001 P<0.001

Change in 6-minute walking distance (m)

FCM

Placebo

Weeks after randomization

KCCQ overall score

P<0.001 P<0.001 P<0.001

Change in overall KCCQ score

FCM

Placebo

Weeks after randomization

EQ-5D VAS score

P<0.001 P<0.001 P<0.001

Change in EQ-5D visual assessment score

FCM

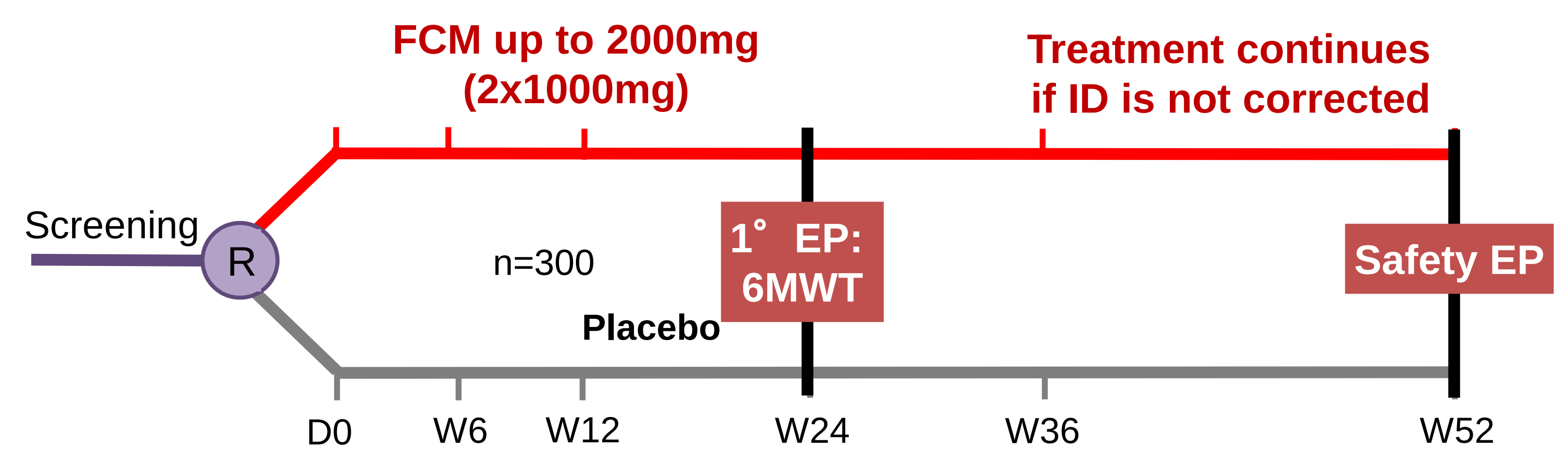
Placebo

Weeks after randomization

Anker *et al*, *NEJM* 2009;361:2436-2448

CONFIRM-HF





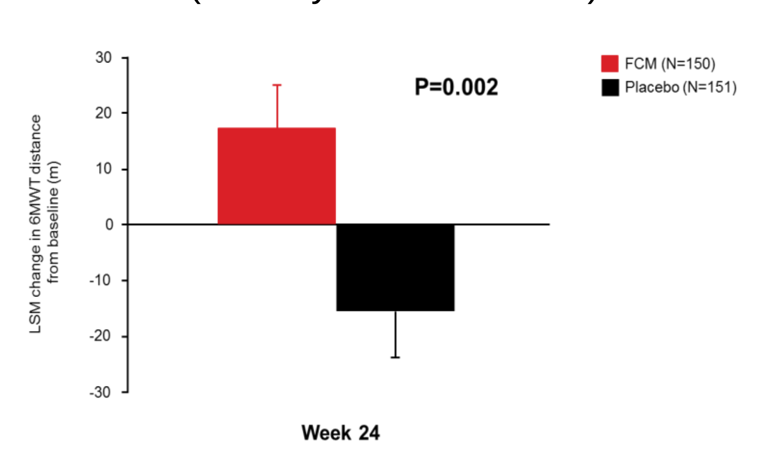
- **Design**
  - Multicentre, randomized (1:1), double-blind, placebo-controlled
- **Main inclusion criteria**
  - NYHA class II / III, LVEF ≤45%
  - BNP > 100 pg/mL or NT-proBNP > 400 pg/mL
  - **Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%**
  - Hb≤ 15 g/dL
- **Primary endpoint**
  - Exercise capacity: change in 6MWT distance from baseline at week 24
- **Secondary endpoints**
  - Change in biomarkers for iron deficiency, cardiac biomarkers, NYHA functional class, PGA and QoL
  - Overall safety over the treatment period

Ponikowski P *et al.* (2014)

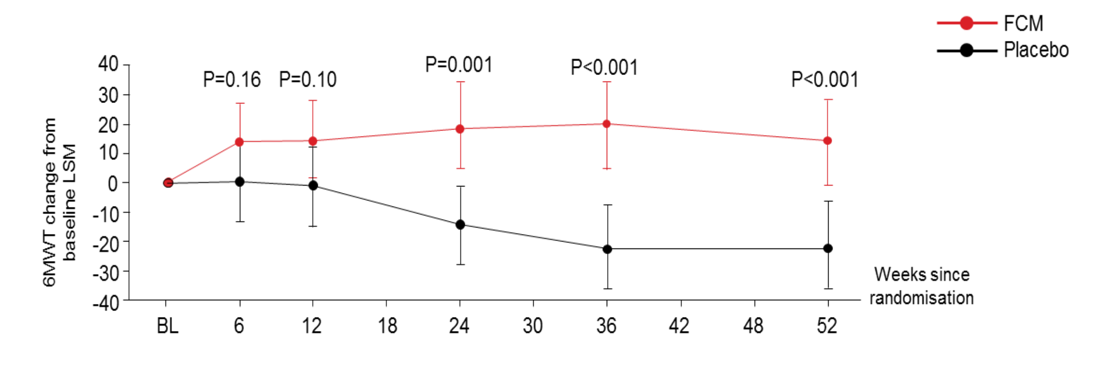
Improvement of 6MWT, NYHA, PGA, QoL and Fatigue



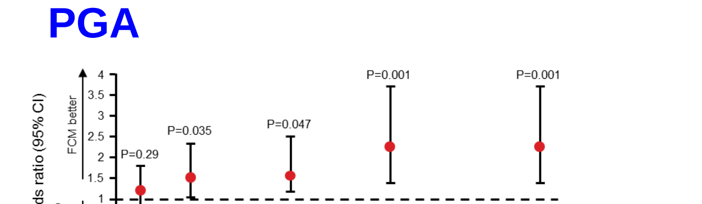
6MWT (Primary EP at Week 24)



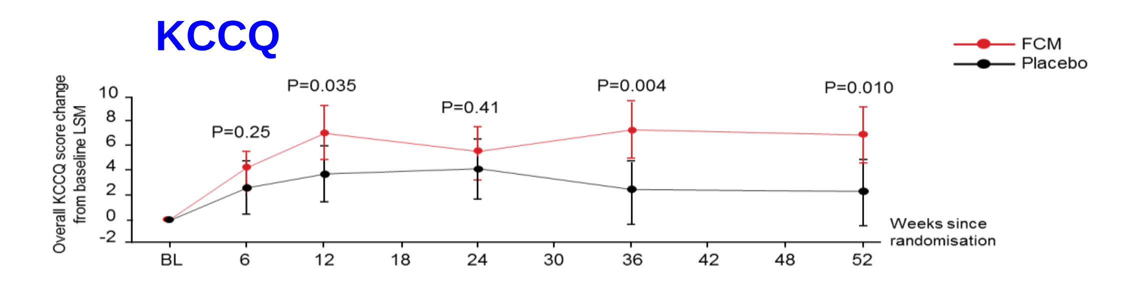
6MWT over time



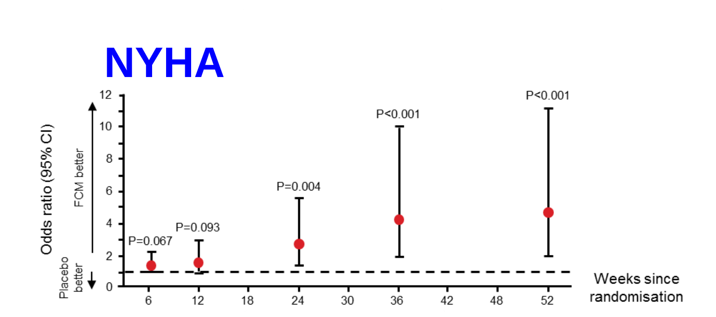
PGA



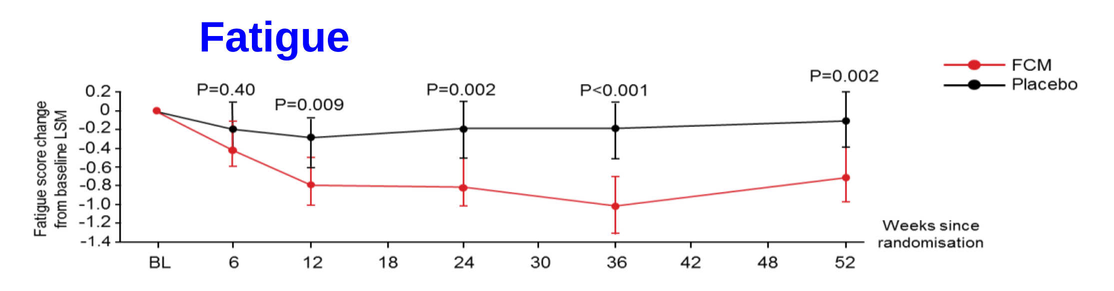
KCCQ



NYHA



Fatigue



Ponikowski P et al. *Eur Heart J* 2015;36:657-68.



Secondary endpoint:
First hospitalization due to worsening HF

Cumulative Hospitalization Rate (in %)

Placebo

FCM

Log–rank test P=0.009

30
20
10
0

0 90 180 270 360

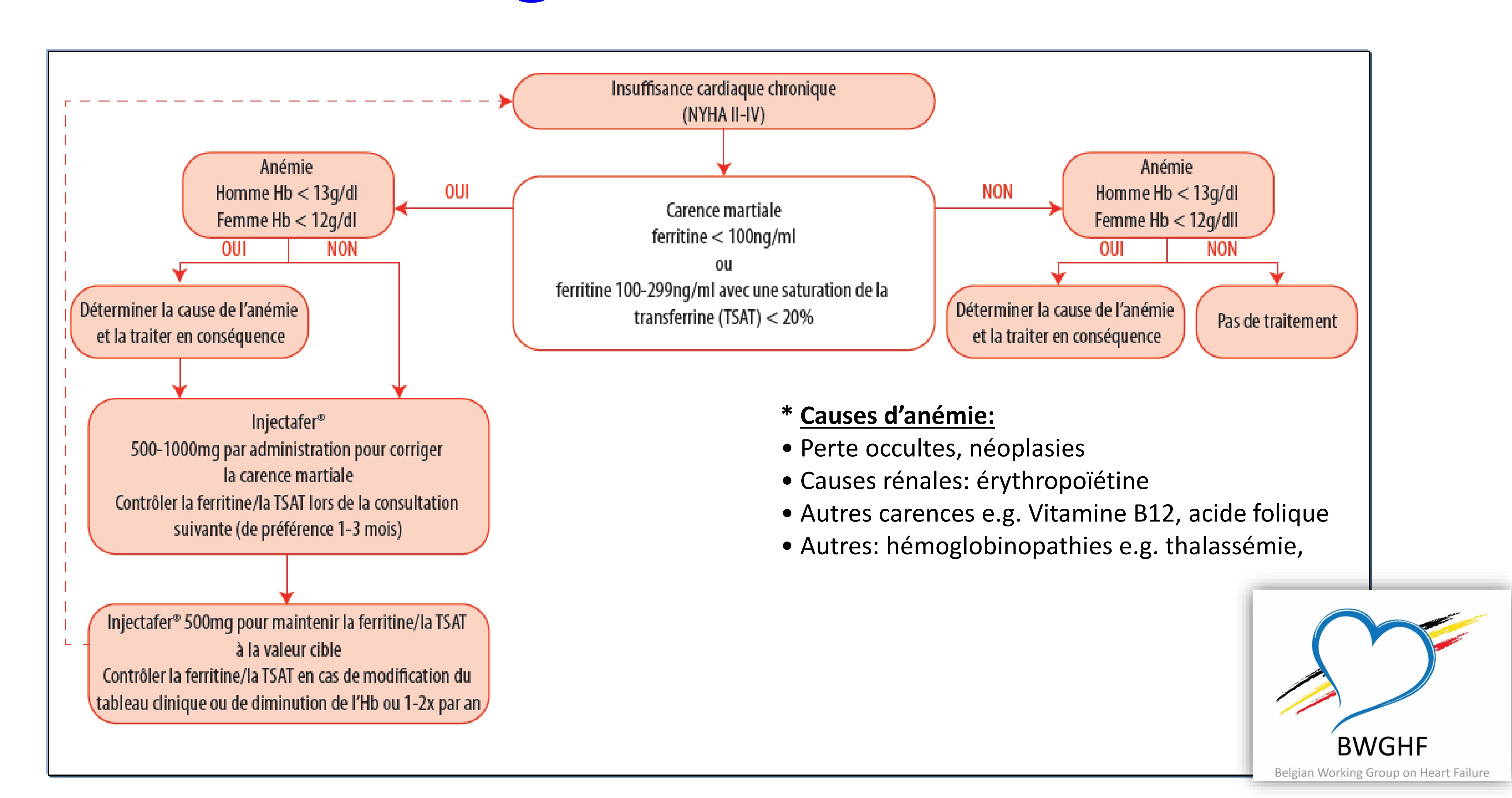
Time (days)

No. of subjects at risk

Placebo	151	138	127	117	78
FCM	150	140	131	126	77

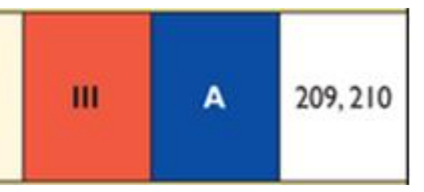
Ponikowski P, et al. *Eur Heart J* 2015;36:657-68.

Prise en charge de la Carence Martiale



DIABETE

ACE-I and ARB ß blockers	prevent/delay DM safe & effective in patients ±DM
Metformin: IIa C	safe to use in CHF & should be treatment of choice, except in severe renal or hepatic impairment
Glitazone	not to be used III A (section 11)

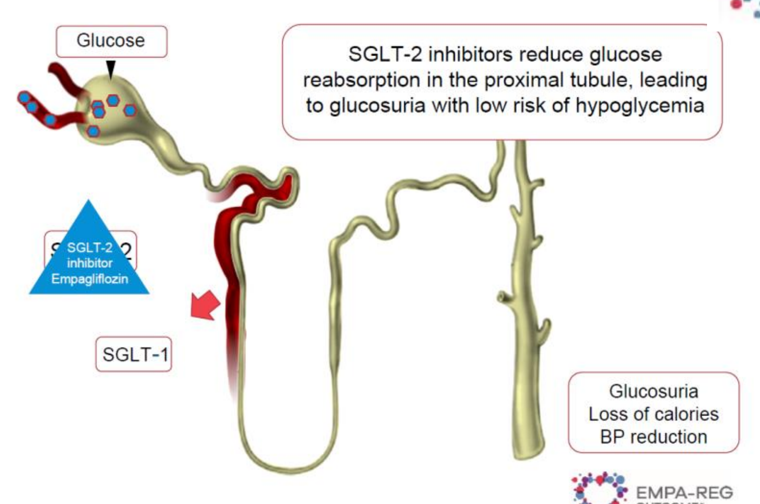


Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	A	209, 210

Empaglifozin

Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B

Mode of action



EMPA-REG OUTCOME®

Outcomes in patients with and without heart failure

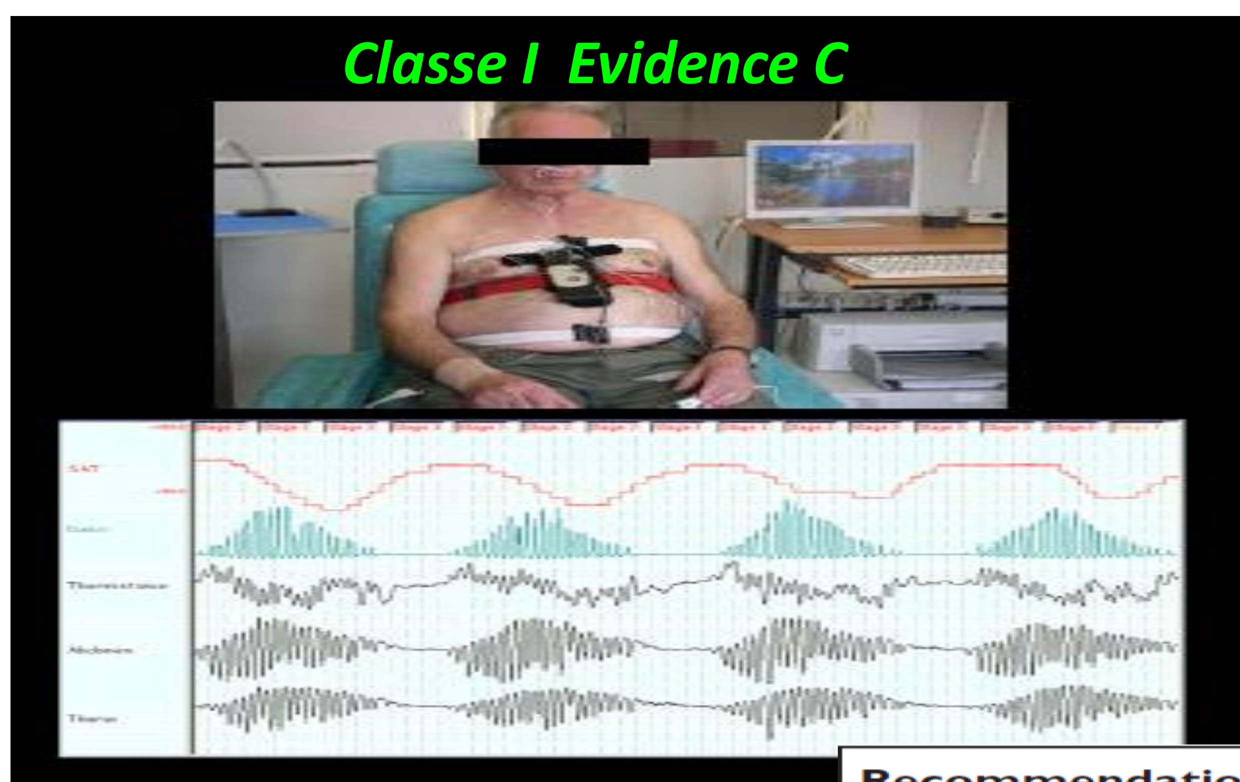
	Empagliflozin No. of patients with event/ no. of patients	Empagliflozin %	Placebo No. of patients with event/ no. of patients	Placebo %	Hazard ratio (95% CI)
Heart failure hospitalization or cardiovascular death					
All patients	265/4687	5.7	198/2333	8.5	0.66 (0.55–0.79)
Heart failure at baseline					
No	190/4225	4.5	149/2089	7.1	0.63 (0.51–0.78)
Yes	**75/462**	**16.2**	**49/244**	**20.1**	**0.72 (0.50–1.04)**
Hospitalization for heart failure					
All patients	126/4687	2.7	95/2333	4.1	0.65 (0.50–0.85)
Heart failure at baseline					
No	78/4225	1.8	65/2089	3.1	0.59 (0.43–0.82)
Yes	**48/462**	**10.4**	**30/244**	**12.3**	**0.75 (0.48–1.19)**
Cardiovascular death					
All patients					
Heart failure at baseline	172/4687	3.7	137/2333	5.9	0.62 (0.49–0.77)
No	134/4225	3.2	110/2089	5.3	0.60 (0.47–0.77)
Yes	**38/462**	**8.2**	**27/244**	**11.1**	**0.71 (0.43–1.16)**
All-cause mortality					
All patients	269/4687	5.7	194/2333	8.3	0.68 (0.57–0.82)
Heart failure at baseline					
No	213/4225	5.0	159/2089	7.6	0.66 (0.54–0.81)
Yes	**56/462**	**12.1**	**35/244**	**14.3**	**0.79 (0.52–1.20)**

Favors empagliflozin — Favors placebo

0.25 0.50 1.00 2.00

Hazard ratio (95% CI)

Recherche des S.A.S.
Troubles du Sommeil

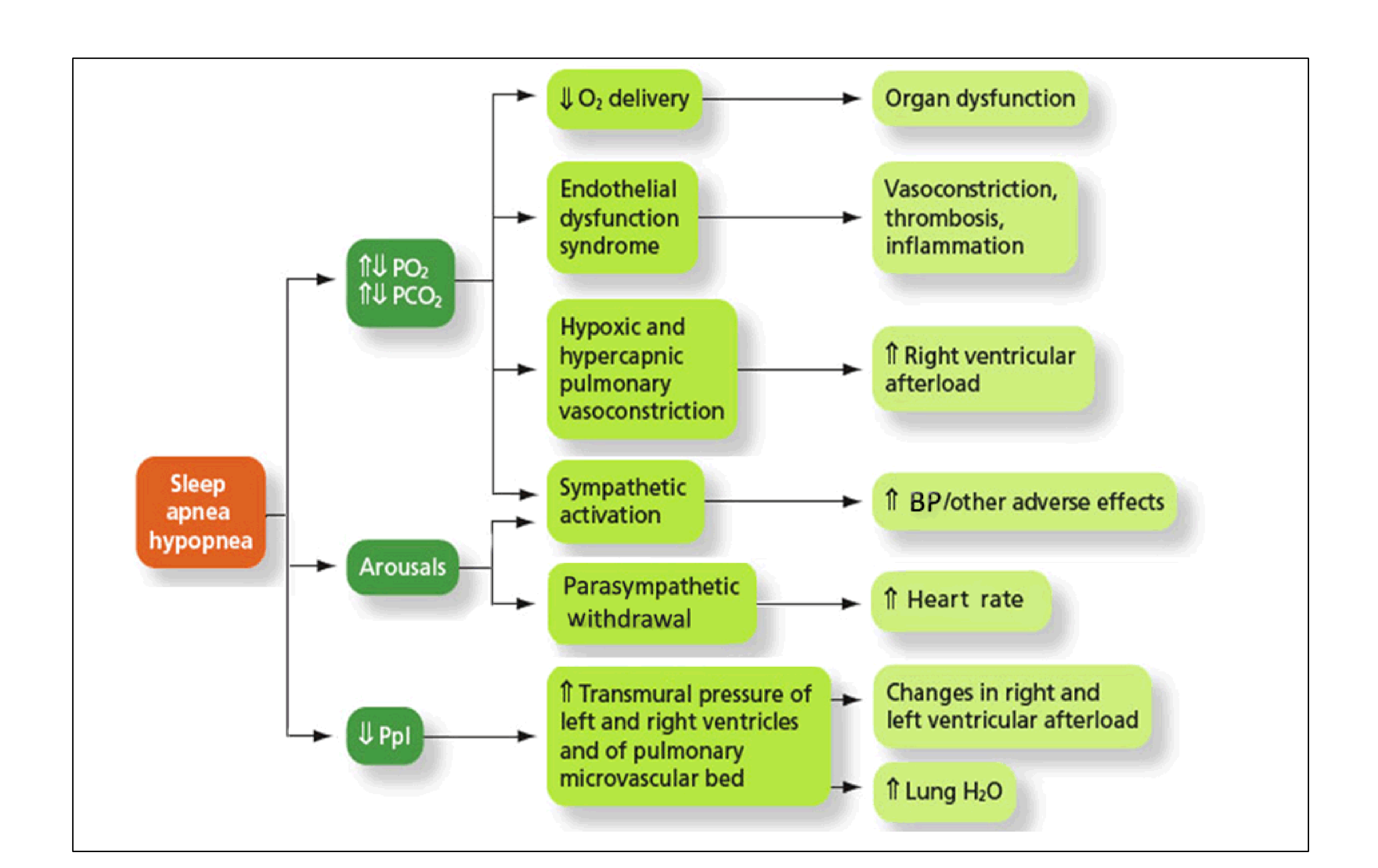


Un index apnée/hypopnée (**AHI**) de **plus de 30 par heure** peut être traité par CPAP, BiPAP and supplementation nocturne en oxygène

Etude SERVE-HF

Recommendations	Class [a]	Level [b]	Ref [c]
Sleep apnoea			
Adaptive servo-ventilation is not recommended in patients with HFrEF and a predominant central sleep apnoea because of an increased all-cause and cardiovascular mortality.	III	B	473

Conséquences des S.A.S.



Transplantation & assistance cardiaque

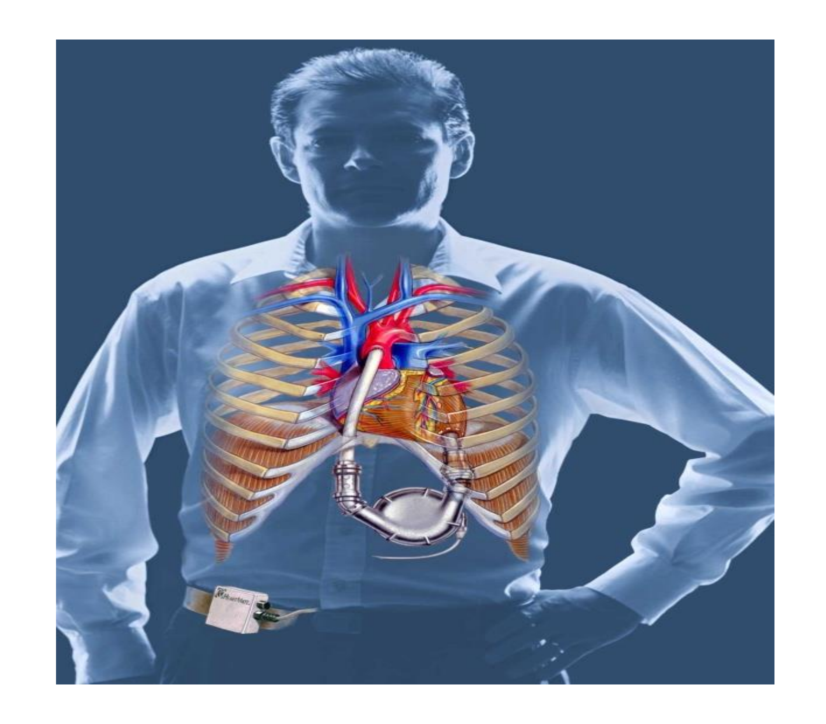
Sélection des patients

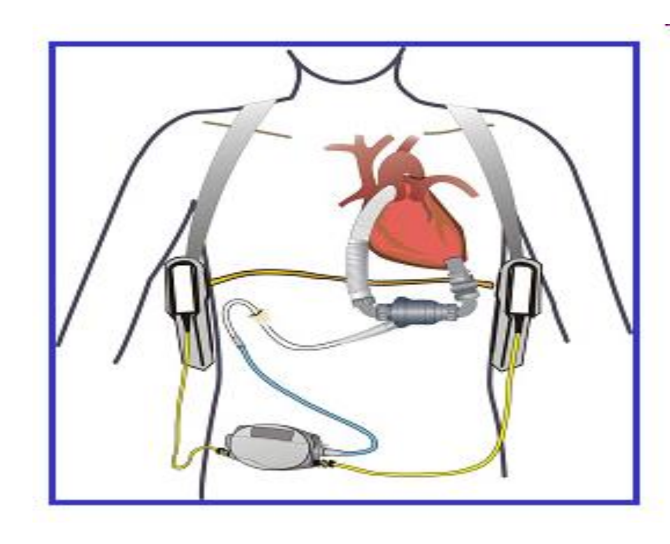
Traitement médical optimisé (± assistance pour les cas les plus graves)

Attendre une réversibilité : sidération post-ischémique, post partum, tachyarythmie, myocardite aiguë, éthylisme…

Principaux critères

- NYHA 3-4
- FEVG < 25%
- Pic de VO2 < 14ml/kg/min
- PCAP > 15mmHg
- Flux mitral restrictif

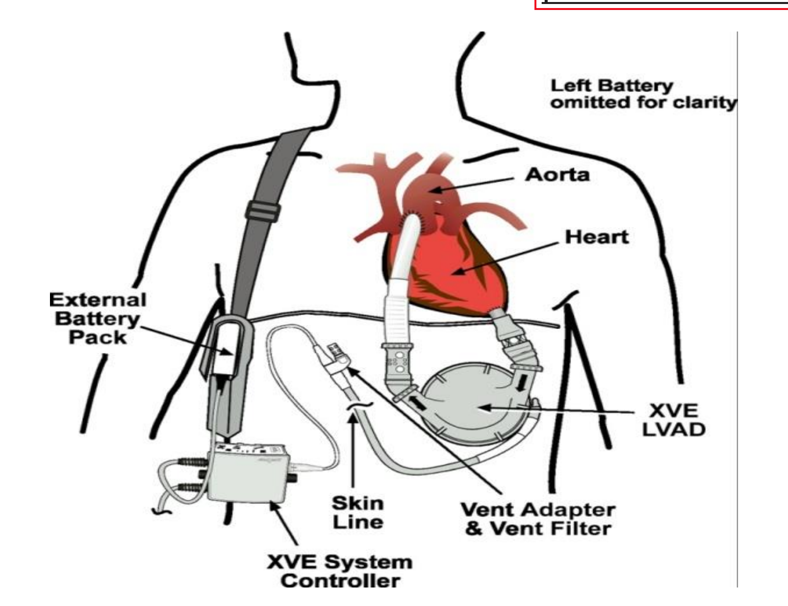


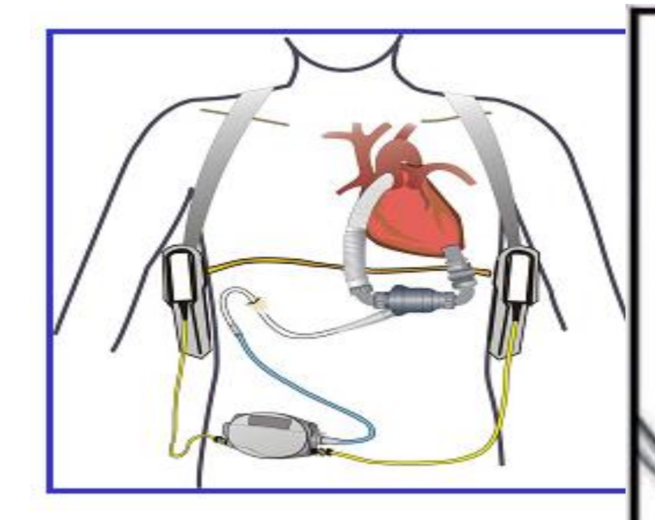


SYSTEMES D'ASSISTANCE VENTRICULAIRE

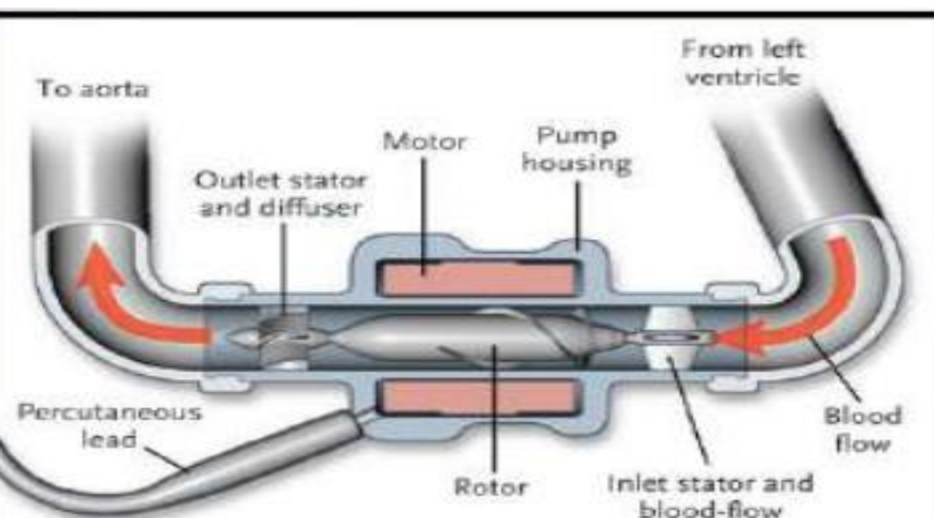
Patients with >2 months of severe symptoms despite optimal medical and device therapy and more than one of the following:
• LVEF <25% and, if measured, peak VO_2 < 12 mL/kg/min
• ≥3 HF hospitalizations in previous 12 months without an obvious precipitating cause
• Dependence on i.v. inotropic therapy
• Progressive end-organ dysfunction (worsening renal and/or hepatic function) due to reduced perfusion and not to inadequate ventricular filling pressure (PCWP ≥20 mm Hg and SBP ≤80–90 mmHg or CI ≤2 L/min/m²)
• Deteriorating right ventricular function

HeartMate XVE
LVAD





HeartMate II



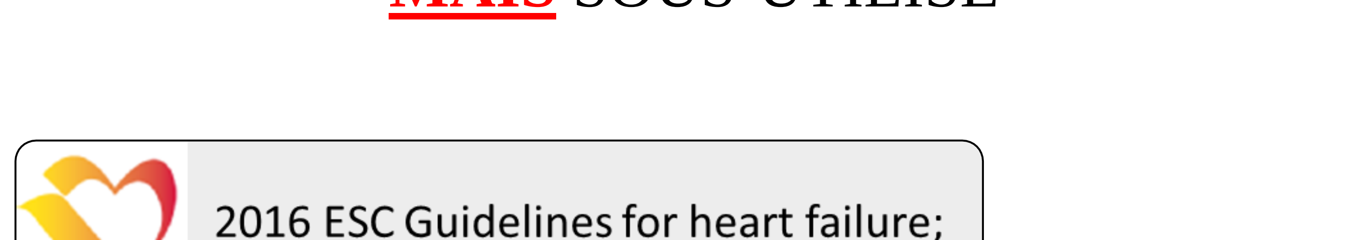
CONCLUSIONS



- I.C. EST FRÉQUENTE
- I.C. TUE
- I.C. EST COUTEUSE



- I.C. EST SOUS-DIAGNOSTIQUÉE
- DEMARCHE DIAGNOSTIQUE & TRAITEMENT ACTUEL BIEN CODIFIÉS **MAIS** SOUS-UTILISÉ





www.bwghf.be

www.escardio.org

Merci de votre attention





Acute Heart Failure: clinical profiles

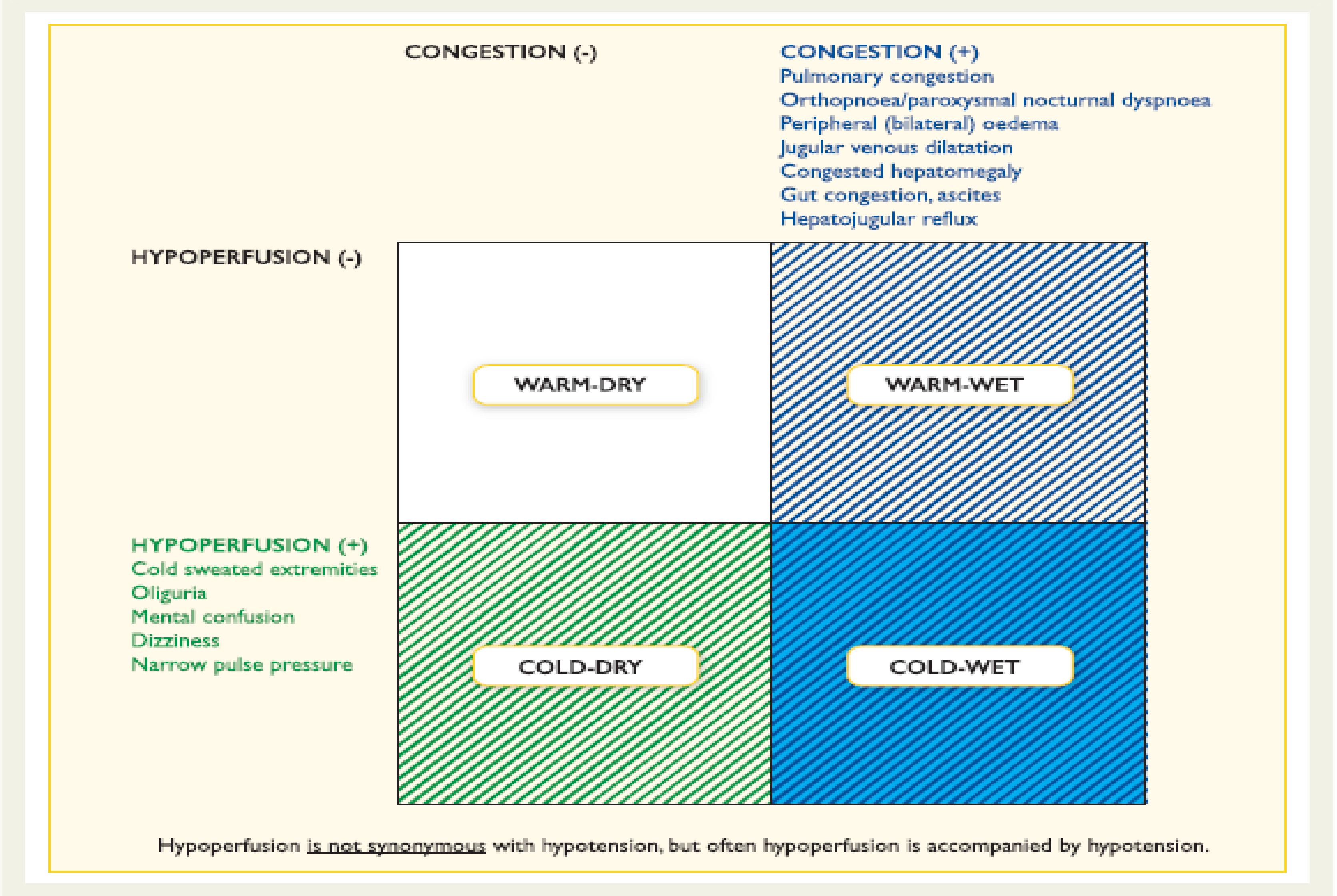


Figure 12.1 Clinical profiles of patients with acute heart failure based on the presence/absence of congestion and/or hypoperfusion

Definition of symptoms in acute heart failure

Table 12.2 Definitions of the terms used in Section 12 on acute heart failure

Term	Definition
Symptoms/signs of congestion (left-sided)	Orthopnoea, paroxysmal nocturnal dyspnoea, pulmonary rales (bilateral), peripheral oedema (bilateral).
Symptoms/signs of congestion (right-sided)	Jugular venous dilatation, peripheral oedema (bilateral), congested hepatomegaly, hepatojugular reflux, ascites, symptoms of gut congestion.
Symptoms/signs of hypoperfusion	Clinical: cold sweated extremities, oliguria, mental confusion, dizziness, narrow pulse pressure. Laboratory measures: metabolic acidosis, elevated serum lactate, elevated serum creatinine. Hypoperfusion is not synonymous with hypotension, but often hypoperfusion is accompanied by hypotension.
Hypotension	Systolic BP <90 mmHg
Bradycardia	Heart rate <40 bpm
Tachycardia	Heart rate >120 bpm
Abnormal respiratory effort	Respiratory rate >25 breaths/min with use of accessory muscles for breathing, or respiratory rate <8 breaths/min despite dyspnoea.
Low O_2 saturation	O_2 saturation (SaO_2) <90% in pulse oximetry Normal SaO_2 neither excludes hypoxaemia (low PaO_2) nor tissue hypoxia.
Hypoxaemia	O_2 partial pressure (PaO_2) in arterial blood <80 mmHg (<10,67 kPa) (blood gas analysis).
Hypoxaemic respiratory failure (type I)	PaO_2 <60 mmHg (<8 kPa)
Hypercapnia	CO_2 partial pressure ($PaCO_2$) in arterial blood >45 mmHg (>6 kPa) (blood gas analysis).
Hypercapnic respiratory failure (type II)	$PaCO_2$ >50 mmHg (>6,65 kPa).
Acidosis	pH <7.35
Elevated blood lactate	>2 mmol/L
Oliguria	Urine output <0.5 mL/kg/h

BP = blood pressure; bpm = beats per minute; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood; PaO_2 = partial pressure of oxygen in arterial blood; SaO_2 = oxygen saturation.

Initial management of the patient with acute heart failure

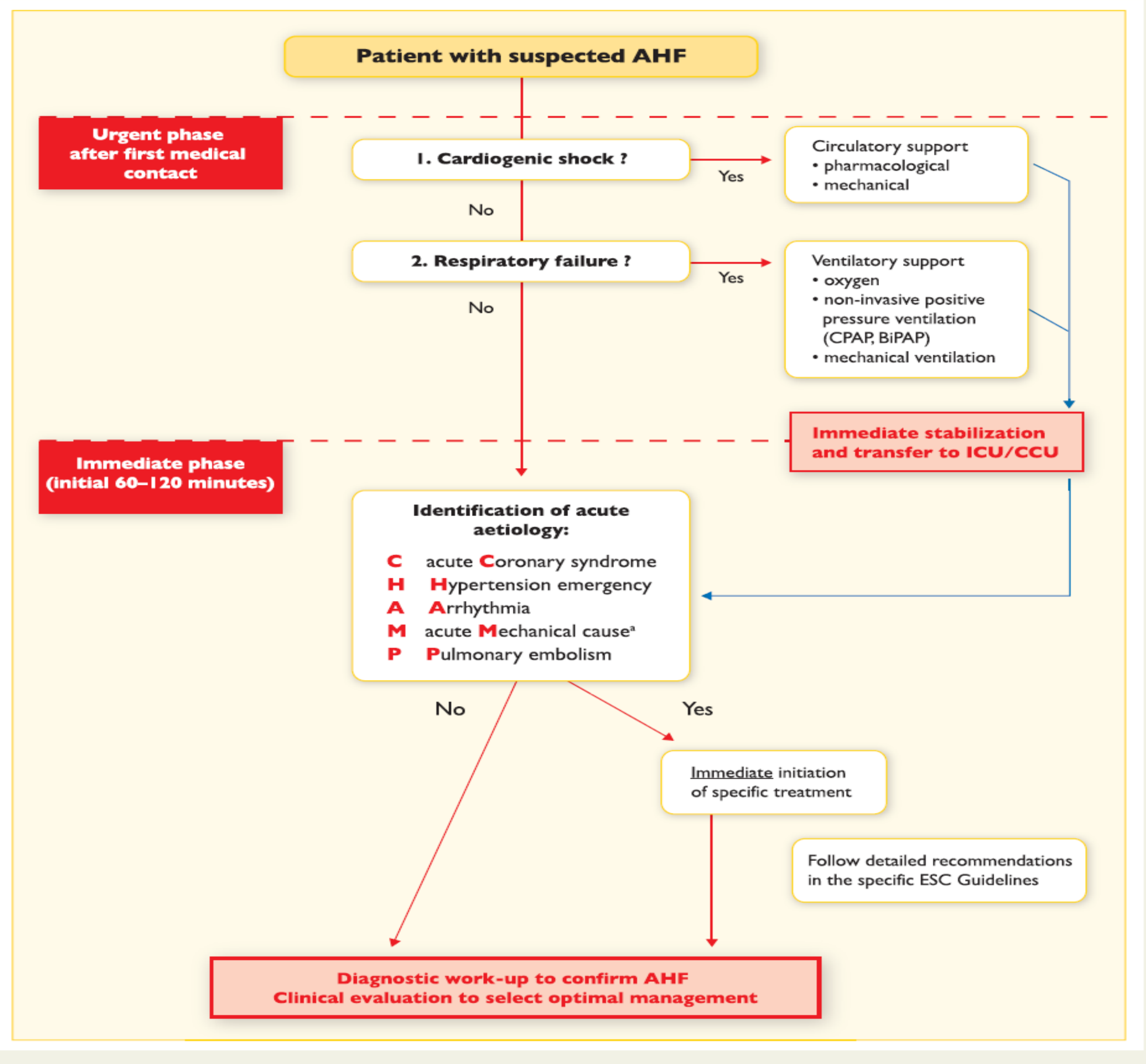


Figure 12.2 Initial management of a patient with acute heart failure. [a]Acute mechanical cause: myocardial rupture complicating acute coronary syndrome (free wall rupture, ventricular septal defect, acute mitral regurgitation), chest trauma or cardiac intervention, acute native or prosthetic valve incompetence secondary to endocarditis, aortic dissection or thrombosis, see above.

Management of AHF based on clinical profile during an early phase

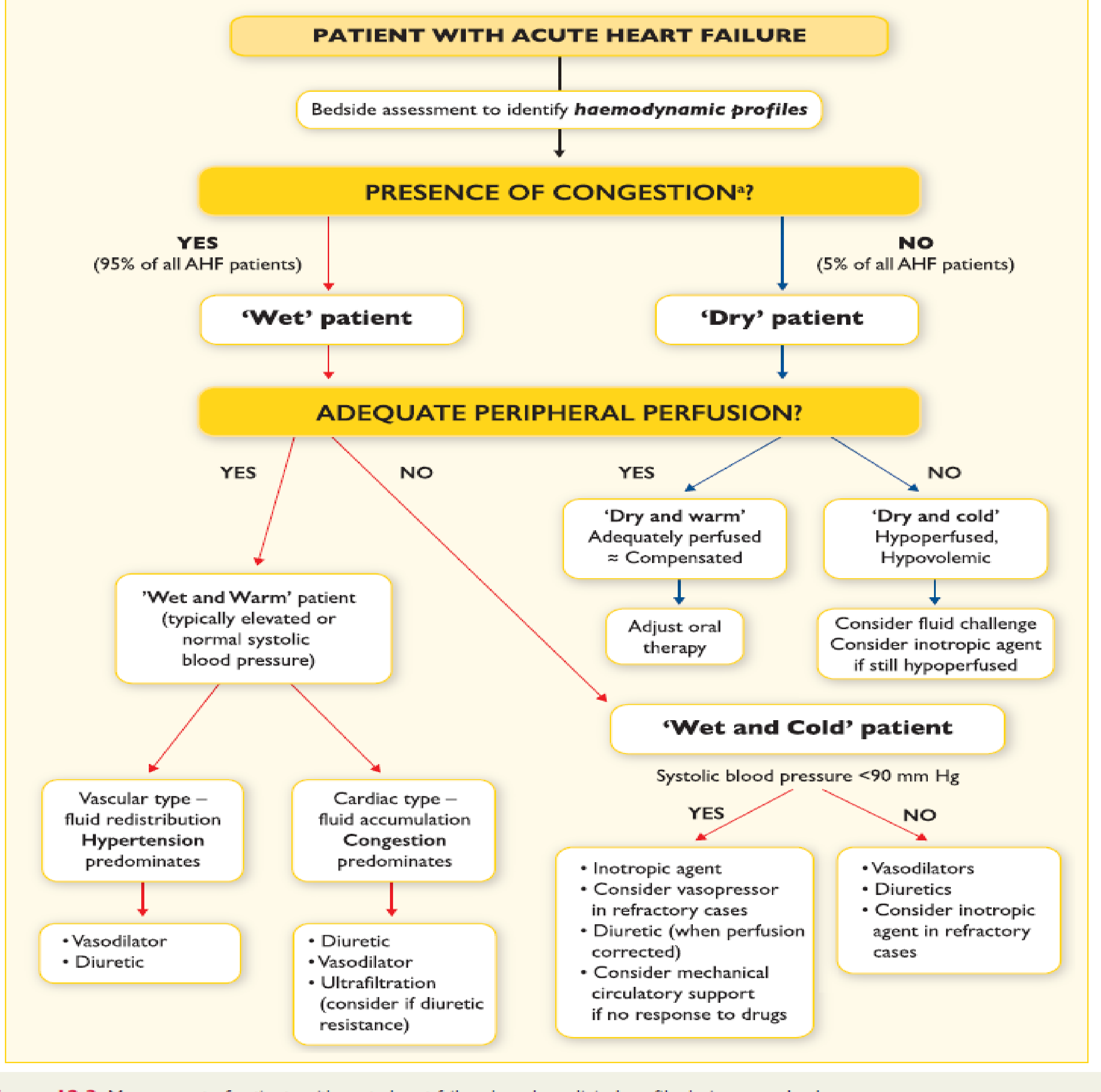


Figure 12.3 Management of patients with acute heart failure based on clinical profile during an early phase
[a]Symptoms/signs of congestion: orthopnoea, paroxysmal nocturnal dyspnoea, breathlessness, bi-basilar rales, an abnormal blood pressure response to the Valsalva maneuver (left-sided); symptoms of gut congestion, jugular venous distension, hepatojugular reflux, hepatomegaly, ascites, and peripheral oedema (right-sided).

